NEWSPAPER POST

TheSynapse

The Medical Professionals' Network

MEDICAL IMAGING

Imaging Hamstring Injury

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Increasing activity in the general population and the high demands placed on athletes have resulted in injuries to the hamstring muscle complex (HMC) being commonplace in sports. The HMC is by far the most frequently injured muscle and is often recalcitrant to even the most meticulous rehabilitation, making HMC injury a significant contributor to athletic morbidity. Knowledge of the HMC anatomy and of the spectrum of imaging findings in HMC injury will enable the musculoskeletal radiologist to make an accurate and useful contribution to the treatment of athletes at all levels of participation. For example tendon avulsion generally requires surgical reattachment, whereas strain patterns of injury are managed conservatively.

Magnetic resonance (MR) imaging and ultrasonography (US) are the imaging modalities of choice for HMC injury as they provide exquisitely detailed information with respect to localization and characterization of injury, assessment of severity and an indication of the prognosis. The portability and availability of US make it an attractive modality for the diagnosis of acute hamstring injuries, but its effectiveness is dependent on operator experience.

Imaging may not be necessary in all cases as clinical data may be enough to reach a diagnosis and decide on treatment. However, in those cases were the diagnosis is unclear or treatment is not achieving the expected results, imaging will provide valuable information about the nature of an injury and the effectiveness of treatment.

Differentiating between injury and muscle soreness, identifying recurrent tears in the rehabilitating athlete, or diagnosing an acute injury against a background of prior chronic strain can be difficult clinically. The latter situation is often clouded by the presence of scar tissue within the muscle. In these situations, imaging particularly with ultrasound is required.

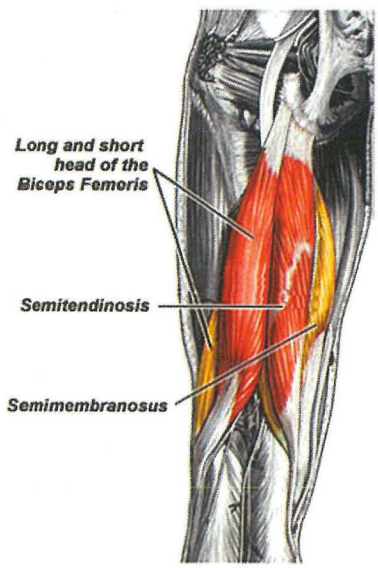

Figure 1. *The HMC is composed of the semimembranosus, semitendinosus and the biceps femoris, the latter having two heads (long and short).*

The three muscles that constitute the HMC lie in the posterior compartment of the thigh and are the biceps femoris, semitendinosus, and semimembranosus muscles (Figure 1).

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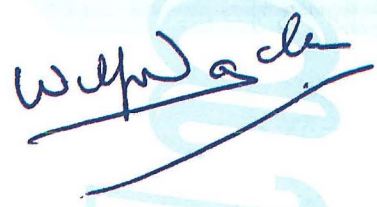
Editor's Word

Welcome to the first issue of TheSYNAPSE magazine for this year. Our organisation is now back again in full swing working on a very ambitious programme for 2008.

Your feedback has been instrumental in maintaining our momentum providing you with a vast range of products and services that are aimed at all professionals working in the medical field. The ultimate aim is none other than helping each reader live a better enriched life and delivering best services to patients.

On behalf of the editorial and production team I would like to thank all contributors as well as advertisers for making this magazine possible.

On my part and on your behalf I would sincerely like to thank our enthusiastic editorial team for putting so much effort in making it happen.



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Imaging Hamstring Injury

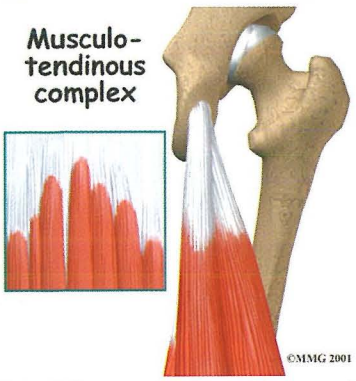

Figure 2. *Proximal attachment of the HMC to the ischial tuberosity and composition of the MTJ.*

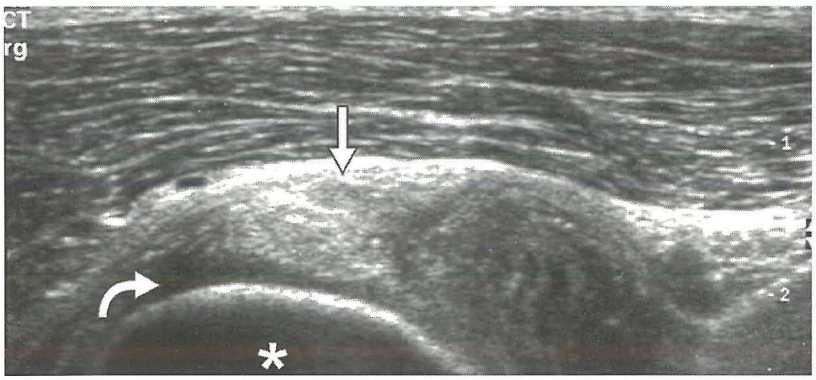

Figure 4. *Sagittal US image shows degeneration of the proximal attachment of the HMC with loss of the normal bright fibrillar echotexture, heterogenous echoes, thickening (straight arrow) and fluid deep to the tendon (curved arrow). * = ischial tuberosity.*

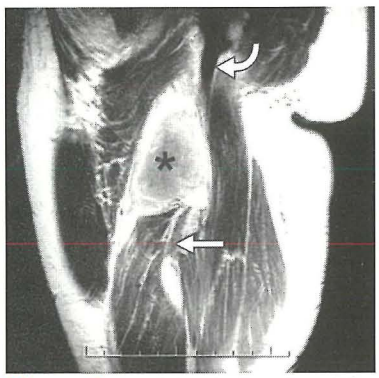

Figure 3. *Avulsion injury in a 29-year-old athlete with a hyperextension injury and persistent disability. Coronal MR image shows a large haematoma (*) with retracted fibres of the semitendinosus muscle and the long head of the biceps femoris tendon (straight arrow). The semimembranosus muscle (curved arrow) remains intact.*

The long head of the biceps femoris and the semitendinosus and semimembranosus muscles attach proximally to the ischial tuberosity (Figure 2). The short head of the biceps femoris originates from the posterior aspect of the femur and therefore does not cross the hip joint. The long and short heads of the biceps receive their nerve supply from two distinct nerves; this separate nerve supply may result in uncoordinated contraction of the two muscle segments and has been suggested as a cause for injury. The distal biceps femoris tendon inserts onto the head of the fibula, the lateral condyle of the tibia, and the fascia of the leg, a rather extensive attachment that is also thought to predispose it to tears. The distal insertions of the semitendinosus and semimembranosus muscles are at the medial aspect of the proximal tibia with extensions deep to the medial collateral ligament of the knee and in 50% of the population with an attachment to the posterior horn of the medial meniscus.

The HMC (or at least most of it) thus acts across two joints, namely the hip and the knee; when it contracts, it extends the hip and flexes the knee. Injury to the HMC occurs during contraction. There are two types of HMC contraction, eccentric and concentric contraction. Concentric contraction occurs during active combined hip extension and knee flexion. While eccentric contraction occurs to stablise (and protect) the knee joint during quadriceps activity; the quadriceps muscles, located in the anterior compartment of the thigh, oppose the HMC in that they cause combined hip flexion and knee extension. Almost all HMC injuries occur during eccentric activity when it contracts while it is being stretched. In addition, the strength of contraction of the HMC is only 60% that of the quadriceps muscles and this imbalance is thought to be a cause for injury. Any condition that diminishes the ability of a muscle to contract (eg, fatigue, weakness or even an old strain or tear) will make the muscle susceptible to injury because it impairs the muscle's ability to absorb force.

continues on page 26

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CONTRAINDICATIONS: Hypersensitivity to zoledronic acid or to any of the excipients or to any bisphosphonate; hypocalcaemia; pregnancy; lactation.

PRECAUTIONS AND WARNINGS: Serum creatinine should be measured before giving Aclasta. Not recommended in patients with creatinine clearance <40 ml/min. Appropriate hydration prior to treatment, especially in the elderly and in combination with diuretics. Use with caution in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration), Pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly advised that patients with Paget's disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget´s disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. A patient being treated with Zometa should not be treated with Aclasta. As a precaution against osteonecrosis of the jaw (ONJ) a dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

INTERACTIONS: Specific drug-drug interaction studies have not been conducted with zoledronic acid. Caution is recommended when Aclasta is used concomitantly with drugs that can significantly impact renal function, such as aminoglycosides and diuretics that can cause dehydration.

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MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

Consult full Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma, P.O. Box 124, Valletta VLT 1000, Malta. Tel +356 22983217.

References: 1. Aclasta SmPC. Novartis Pharma AG. 2. Black DM, Delmas PD, Eastell R, et al; for the HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356:1809-1822. 3. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. *Bone*. 2007;40:1238-1243. 4. McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*. 2007;41:122-128.

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Neural Stem Cells and

by **Charles Scerri** *BPharm (Hons) MPhil PhD (Dundee) MIBiol EurProBiol*
Department of Pathology, Faculty of Medicine and Surgery, University of Malta

Aging is usually associated with progressive loss of central nervous system functions particularly in the presence of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. In the last few years, cell replacement strategies have been put forward in order to repair the brain and replace the lost brain tissue due to disease. However, successful application of such therapies require the full understanding and knowledge of the complex relationships involved between neural stem cells, normal aging and the neuropathology involved.

The human brain has the ability to retain normal function for a considerable number of years. However, the emergence of neurodegenerative disorders associated with old age is becoming increasingly common. For example, the prevalence of Alzheimer's disease increases from 2-3% in individuals having 65 years of age to around 40-45% in those over the age of 85 years.[1] The sharp rise in life expectancy in many developed and developing countries not only leads to the explosive growth in the numbers and proportion of older persons but also in the incidence of neurodegenerative disorders associated with age. It is therefore not surprising that a lot of attention has been devoted to the recent advances in stem cell therapies which can offer the potential of replacing brain cells in the aging and diseased brain.

The Aging Brain

Similarly to other organs, the brain undergoes a progressive decline in function with increasing age.[2] In the central nervous system, normal aging (in the absence of any neuropathology) is associated with altered structural changes. The number of brain cells decreases in many areas of the brain and post-mortem studies indicate a reduction of around 5% in brain volume per decade after the age of 40 years.[3] There is also an increase in the size of the ventricles, shrinkage of several brain areas such as the frontal cortex and the striatum, and loss in the number of synapses, especially in the prefrontal cortex. On a cellular level, aging of the central nervous system is accompanied by a number of changes that impair cellular function. Oxidative stress increases, damage to both DNA and protein accumulates, cellular metabolism is impaired and lipid and protein by-products accumulate in the brain.[4] Mitochondrial function also declines, with an associated increase in mitochondrial DNA oxidation and impairment of DNA repair.[5] A significant number of signal transduction pathways are also altered, leading to reduced efficiency in neurotransmitter release. Although these changes per se do not cause neurodegeneration, they may predispose the brain to pathologies such as Alzheimer's and Parkinson's diseases.

One of the most remarkable changes that occur in the brain is the alteration in cognitive performance. Compared to young individuals, older adults show different patterns of brain activation when performing cognitive tasks. Most notably, there is age-related impairment in short-term memory and cellular repair capacity, with the latter mostly evident in the presence of neurodegenerative disease.

Age-related Neuropathology

Three of the most prevalent age-related neurodegenerative disorders are Alzheimer's disease, Parkinson's disease and stroke. All three share a common feature: specific populations of brain cells are affected. In Alzheimer's disease, a disorder which mainly affects memory and cognitive function, the brain regions mostly affected are the hippocampus and the cerebral cortex. In Parkinson's disease, a disorder associated with loss of motor function, there is selective loss of dopamine-producing cells in the substantia nigra. In stroke, characterised by blockage or rupture of a blood vessel, there is selective loss of brain cells in the area supplied by the damaged blood vessel. Traditional therapies for each of these diseases have focused on pharmacological approaches. Because in Alzheimer's disease there is loss of cholinergic function, pharmacological agents that have been developed sought to enhance cholinergic transmission via the inactivation of enzymes that break down acetylcholine.[6] In Parkinson's disease, therapeutic agents aim to enhance dopaminergic transmission by increasing the levels of its precursor, L-DOPA, or by blocking enzymes responsible for its breakdown or else by direct stimulation of dopamine receptors.[7] In stroke, treatment is usually directed towards minimising the secondary damage that follows injury.

Neural Stem Cells

Recent studies have shown that certain areas of the brain are capable of producing new cells, a process known as neurogenesis. During the course of neural development, there is a progressive restriction in the differentiation capacities of the cell. Therefore, embryonic stem cells have pluripotent characteristics (ability to develop in almost all kinds of cells) whereas tissue stem cells have multipotent characteristics and only differentiate into a subset of cells related to the tissue in which they are present. Neural stem cells can only give rise to three major types of cells in the central nervous system: neurons, astroglia and oligodendrocytes. Under normal conditions, there are several possible outcomes for a neural stem cell. Stem cells may remain quiescent and not undergo division, or may undergo apotosis and cease to exist. Alternatively, stem cells may proliferate to produce new stem cells or else differentiate into a mature brain cell. This outcome is regulated by a variety of factors such as growth factors, receptor expression and neurotrophic factors.

Role of Neural Stem Cells in the Aging Brain

In the adult mammalian brain, neural stems cells are located in two major areas of the brain: the olfactory bulb and the hippocampus. Studies show that age-induced stress factors such as an increase in oxidative stress and DNA damage inhibit the formation of neural stem cells. This is most evident during development. For example, prenatal stress inhibits neurogenesis and affects learning and memory in

the Aging Brain - Part I

the adult hippocampus.[8] Other factors have been found to have a profound effect on neurogenesis including the presence of an enriched environment, exercise, ischemia and antidepressant drug therapy. Neurogenesis also decreases with age even in the absence of any neurodegenerative condition. This is mostly evident in the hippocampus.[9] Neural stems cells may also have a role in age-related diseases of the brain. Amyloid plaques, which play an important role in the pathology of Alzheimer's disease, not only inhibit the proliferation of neural stem cells but also promote apoptotic cell death. Individuals with early-onset Alzheimer disease (of which a genetic component is the main contributor) exhibit as much as 75% loss of neurons in the olfactory bulb leading to a significant loss of smell.[10] A decrease in the proliferation of neural stem cells in the hippocampus may also contribute to the pathology of Alzheimer's disease and the associated loss of cognitive functions.

References

1. Scerri C. The face of dementia. BOLD – *Journal of the International Institute of Ageing* 2005; 15(3):19-22.

2. Persson J, Nyberg L. Altered brain activity in healthy seniors: what does it mean? *Prog Brain Res* 2006; 157:45-56.

3. Kemper T. Neuroanatomical and neuropathological changes during aging and in dementia. In: Albert M, Knoepfel J, editors. *Clinical Neurology of Aging. New York: Oxford University Press*; 1994. 3-67.

4. Humphries KM, Szweda PA, Szweda LI. Aging: a shift from redox regulation to oxidative damage. *Free Radic Res* 2006; 40:1239-43.

5. Sastre J, Pallardo FV, Vina J. Mitochondrial oxidative stress plays a key role in aging and apoptosis. IUBMB *Life* 2000; 49:427-35.

6. Scerri C. Pharmacotherapeutic approaches in the treatment of Alzheimer's Disease. *J Malta Coll Pharm Pract* 2006; 11:8-10.

7. Bonuccelli U, Del Dotto P. New pharmacologic horizons in the treatment of Parkinson's disease. *Neurology* 2006; 67(7 Suppl 2):S30-8.

8. Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 1996; 726:49-56.

9. Montaron MF, Petry KG, Rodriguez JJ et al. Adrenalectomy increases neurogenesis but not PSA-NCAM expression in aged dentate gyrus. *Eur J Neurosci* 1999; 11:1479-85.

10. Devanand DP, Michaels-Marston KS, Liu X et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiat* 2000; 157:1399-1405.

Depression during pregnancy

by **Ethel Felice** *MD BCPsych MPhil*
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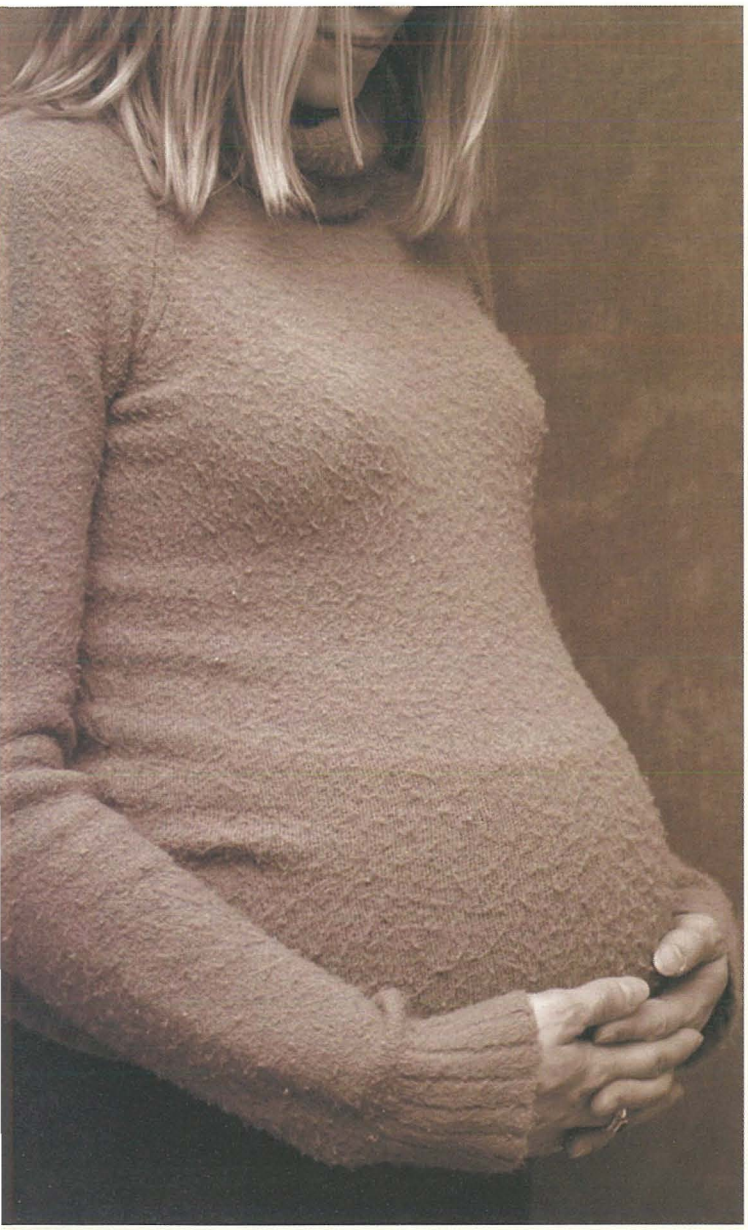

In recent years much more attention has been paid to postnatal mental illness and to its possible effects on the baby than to antenatal mental disorder and its effects on foetal development.[1] It is now generally accepted that most women do not conform to the stereotype of the woman who blooms with health in pregnancy.[2] Observers have commented on the apparent high prevalence of psychiatric symptoms in pregnancy. Studies of antenatal depression offer certain advantages. The time perimeter is limited to the pregnancy, easing comparisons between studies. Furthermore women can easily be recruited since pregnancy is a time of high medical contact.

Incidence and prevalence of antenatal depression

Studies on the incidence of antenatal depression have revealed that it is higher than previously thought. O'Hara found that 9% of pregnant women have illnesses that fulfill the Research Diagnostic criteria for depression.[3] Similarly, Scholle screened obstetric patients at random for depressive symptoms and found that 20% met criteria for a diagnosis of depression.[4] It is now believed that pregnancy is a risk factor for a mood disorder especially in those with a history of depressive illness,[5] and untreated antenatal depression may be associated with 50-62% of postpartum episodes and a worsening of the psychiatric condition.[6,7]

Variables associated with antenatal depression

It is important to identify the causes of prenatal depression. Most of the studies carried out found an association with psychosocial factors. Depression during pregnancy is associated with being younger, less educated, having a greater number of children and being a home maker[8], previous termination of pregnancy, having serious doubts about having the baby, having anxieties about the foetus[2], having an unwanted pregnancy and a negative psychological response to the news of the pregnancy by the woman and husband.[9] Evidence of personal past psychiatric disturbance in the mother, premorbid neurotism, marital conflict and lack of support were also associated with antenatal depression.[2]

Effects of antenatal depression

Depression in the antenatal period is usually missed. Depressed women are not good antenatal attendees. Depressive symptoms were associated with poor weight gain and may have caused poor health behaviour such as cigarette smoking, alcohol and drug abuse[10] Antenatal stress and smoking contributed independently and significantly to a lower gestational age, lower birth weight and smaller head circumference when corrected for birth weight.[11] Prenatal stress also worsened the scores on the neonatal neurological examination.

Antenatal depression may cause ill adjustment to pregnancy and is also likely to affect the course of pregnancy. The effect can also be on the physical welfare of the foetus. Behavioural responses may be developed by the foetus from quite early in gestation. Studies found that the foetus could mount its own hormonal and other stress responses from at least mid-gestation. The mechanism for transmission of maternal stress on the foetus is not known. Possible mechanisms described include constriction of the uterine artery by maternal stress hormones causing impaired blood flow to the baby, which in turn generates a foetal stress response.[12] Also certain hormones are transmitted in sufficient amount to the foetus to have a direct effect.[13] Despite the prevalence of depression during pregnancy and the amount of literature associated with its treatment, whether pharmacological or otherwise, large numbers of women are untreated. In one study, one in five pregnant women experienced depression but few sought treatment.[14] Such studies conclude that the stigma of having depression during pregnancy may prevent women from seeking active treatment – women may feel guilty for suffering during what is supposed to be a happy period.

continues on page 18

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The vaccine should be administered by intramuscular injection. The preferred site is the deltoid area of the upper arm or in the higher anterolateral area of the thigh.Silgard must not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and therefore are not recommended. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Silgard should not receive further doses of Silgard. Administration of Silgard should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation. **Warnings and precautions:** As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.As with any vaccine, vaccination with Silgard may not result in protection in all vaccine recipients.Also, Silgard will only protect against diseases that are caused by HPV types 6, 11, 16 and 18. Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.Silgard has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, high-grade cervical, vulvar and vaginal dysplastic lesions or genital warts. It is also not intended to prevent progression of other established HPV-related lesions. Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Silgard will not provide protection against non-vaccine HPV types, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations. There are no data on the use of Silgard in subjects with impaired immune responsiveness. Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine.This vaccine should be given with caution to individuals with thrombocytopaenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. The duration of protection is currently unknown. Sustained protective efficacy has been observed for 4.5 years after completion of the 3-dose series. Longer term follow-up studies are ongoing The data on Silgard administered during pregnancy did not indicate any safety signal. However, these data are insufficient to recommend use of Silgard during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy. Silgard can be given to breastfeeding women. **Undesirable effects:** Very common: pyrexia and at the injection site: erythema, pain, swelling. Common: at the injection site: bleeding, pruritus. In addition, in clinical trials adverse reactions that were judged to be vaccine- or placebo-related by the study investigator were observed at frequencies lower than 1%: rare: urticaria and very rare: bronchospasm.
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Fourth and last letter from Your Clinical Psychologist

by **Paul Micallef** *BA DClinPsych CPsychol(UK)*
Chartered Clinical Psychologist &
Consultant/Advisor for Staff Training and Retraining

Dear Colleague,

In the last three issues of TheSynapse Magazine I wrote a series of letters focusing on personal well being and self care. The introductory letter looked at how you deserve the same attention, understanding and treatment on self care which is often recommended to others. I believe this is important given health predictions, concerns and evidence that cardiovascular disease, cancer and what I term "mysteriously undefined illnesses" which in my opinion are directly linked to stress and are on the increase worldwide.

Outlined in the first letter was one of the fundamental building blocks of self care, intra-personal communications. This is often one of the most difficult tasks to achieve in life because we are rarely trained or guided in how to communicate with ourselves in a healthy and balanced way. Instead, most of our energies are focused on helping others improve their quality of life, or helping them die with dignity. We are excellent at giving advice but when it comes to ourselves, and our own personal and holistic interests, we falter.

The second letter linked the area of intra-personal communication to expectations. Here, I outlined a direct link between our thoughts, emotions and behaviours. I invited you to occasionally take time to consider and reflect on the power of personal thoughts and perceptions implying that expectations are another significant factor in the self care equation. In this letter, the message was that one has to constantly work on positively reframing thoughts and perceptions so that expectations remain realistic, fair and reasonable over time.

In autumn, just before and during a number of major changes within our health care sector, I wrote about assertiveness. The changes I refer to include the migration of services from St Luke's to Mater Dei Hospital; the extension of Zammit Clapp services into Karen Grech Hospital; the total reorganization of the management structure at the Ministry of Health, Elderly and Community Care and the appointment of new administrative directors; the signing of two agreements between MAM and MUMN and the Government; and the introduction of the Pharmacy-of-Your-Choice scheme. All this happened in a matter of months whilst the country was also experiencing a major change in terms of the introduction of a new currency, the euro.

When I wrote about assertiveness the idea was to promote the use of a coveted skill that helps us in managing change and transitions more competently. In fact, at the end of the third letter I promised that in this fourth and last letter I would focus on changes and transitions. I am doing this because I believe that assertiveness will help us handle the challenges such changes and transitions trigger. I trust you are aware that such challenges have the potential of jeopardizing or sabotaging our efforts to achieve a healthy work life balance that in turn allows us to cope with the stress and burnout which activate the very illnesses that we and colleagues also succumb too as any other human being.

I sincerely doubt whether our health care sector has ever experienced, or will ever see, so much flux and instability at the same time. What complicates our scenario is the fact that these changes are taking place in a wider national context that in itself is also experiencing momentous change. What encourages me to share some of my thoughts is the fact that I believe you can help improve the situation. Apart from helping yourself achieve better personal self-care, I believe that you can also be instrumental in helping others around you achieve a better work-life balance.

I imagine that many of TheSynapse readers are actually in a position of leadership or management both in society and within our health care system. In my opinion, this triggers a double obligation. One is towards ourselves as human beings and the other is towards those for whom we are either responsible or accountable for. These include our family, friends, colleagues and patients. An understanding and appreciation of the impact changes and transitions have on people is another strategic tool in your self care tool box. This understanding helps us plan better and take wiser decisions to prevent an incredible amount of potentially negative personal and work related stress from piling up.

Change is situational and mostly directed towards achieving a result. Change often addresses the 'physical' and structural dimensions of a situation. For example starting a new job, retiring, moving house and becoming a parent are all changes. These changes are different from the transitions and adjustments people have to make and go through over time and once the change actually occurs. Transitions are about processes. In contrast to situational events which happen quickly and in short time frames, transitions take longer. They involve thoughts and attitudes which in turn heavily influence the way we feel and behave.

It is understandable and expected that human beings require time to first appreciate changes which directly impact on their well being. This is a process which requires space and time and does not come at the push of a button or without previous planning and preparation. I believe that transitions and adjustments deserve their due respect because they have the power to totally devastate and ruin any brilliantly laid out plan or strategy. It would be foolish to underestimate the power of human factors be it at home or work.

It is only when changes are understood at an intra-personal level that a human being can move on to healthy and constructive inter-personal communications that take other people and situations into account. Successful inter-personal communications always require assertiveness as the main tool to achieve positive outcomes.

More specifically, transitions require that we as human beings let go of the way things used to be and work, and take on new or different ways in which they subsequently become. By simply informing, instructing or ordering people to do things in a new or different way or by transferring them from one building to another does not in any way address the transitions and adjustments people need or have to make over time. I imagine you have moved home or changed jobs at least once in your lifetime and therefore know what I am referring to. Human beings need time to adjust and in this time they need to communicate their thoughts, wishes, needs, desires, fears, anxieties, expectations, losses and excitement. This is the work that needs to take place regularly and during a transition process.

continues on page 10

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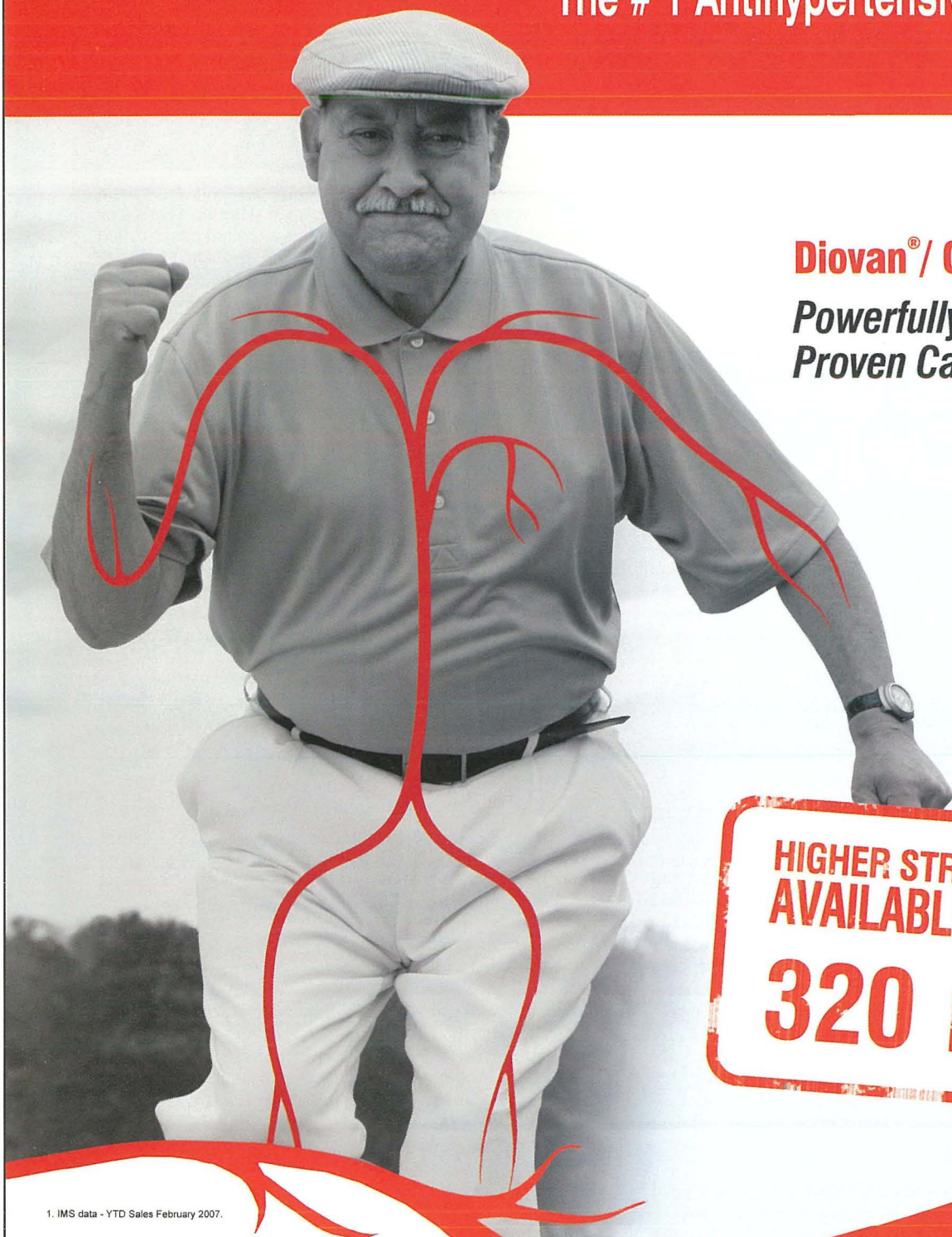

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Fourth and last letter from Your Clinical Psychologist

continued from page 8

In themselves, transitions are somewhat paradoxical because to achieve successful results we have to be willing to change and let go of how things used to be. The very things which we wish to hold onto, to control and keep safe, are in themselves the products of change. Children are a brilliant example. No matter how much we want them to grow up and mature, we are also plagued by fear of what will happen when they do grow up. For example, we worry what will happen when they start going out on their own, when they take their first holiday abroad or when they start driving. All are natural changes which we support and wish them well with but why then are so many parents riddled with anxiety when the time comes for these changes to occur?

Transitions last longer than change. If addressed healthily, it is not unusual for successful transitions to last several months. Obviously, the magnitude of the change influences the time needed for a transition. What happens is that change triggers a range of thoughts and emotions that in turn trigger behaviours which at times are positive but could also be negative. If left unaddressed, these negative thoughts and emotions can seriously sabotage and jeopardize the very change we want and many of us work hard to achieve. Whether it is resistance, ambivalence, uncertainty, ambiguity or fear of communication (often disguised by lack of time), allow me to repeat how important it is to regularly address intra- and inter-personal dynamics in the transition process.

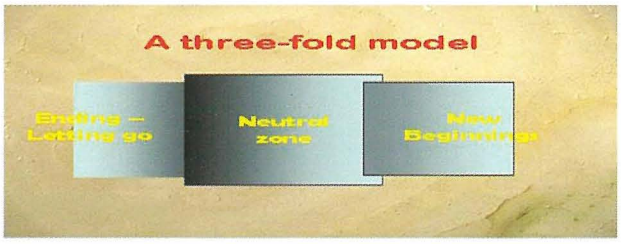
Transitions have the capacity of threatening or exposing us and as a result trigger unresolved past issues and personal problems that strongly **resonate** with current changes. This **resonance** allows people to camouflage past unfinished and unhealthy business with new situations. Issues which would have literally lain unaddressed for a very long time suddenly surface because they are directly and in an unhealthy manner linked to the new experiences. Thus the very result which the change is trying to achieve is swiftly overwhelmed and unnaturally burdened by issues that do not really belong to current changes or the transition process. Remaining mindful of the fact that when reactions to change surface, especially when they are overwhelming and seriously threatening the desired change, it is possible that unresolved and past destructive forces have found a convenient way to surface for attention.

Anne Morrow Lindbergh states that "There is no sin punished more implacably by nature than the sin of resistance to change". Thus, finding a way to cope with transitions, be they reactive or developmental, is useful. Common and fool proof strategies include on-going individual face-to-face meetings which are structured and not simply happen by chance, regular family or team meetings that are also structured and not left to chance, occasional away days to address core needs and how these needs link in with the general destination and direction being taken by the family/team, and honest and open discussions that happen naturally and over time that highlight genuine thoughts, emotions and consequent behaviours. This work needs to be done in a natural and unthreatening manner. The important thing is that we truly listen and understand what we are saying to ourselves and others, and what others are saying to us. To prove this, feedback is the best insurance going in communications. Joint action plans that respect human factors whilst at the same time ensuring that work and deadlines are addressed competently and on time also trigger success.

Understanding that we as human beings normally go through three phases when faced by transitions is helpful. The three phase model outlined below highlights an initial phase called "LETTING GO". This helps us understand that when a change happens we are being asked to bring something to an end. Time needs to be taken to recognize this and appreciate what has happened till that point in time. If dealt with successfully, this first phase leads to a "NEUTRAL ZONE" where the situation is often confusing and can become naturally uncomfortable.

In the neutral zone we understand that the usual patterns of behaviours which were good in the past and in previous situations are now no longer valid or equally helpful. We recognize that we have lost certain ways of functioning and new ones are taking shape. This neutral zone is a time when many things are literally up for grabs. At this point, those with responsibility and accountability are obliged to protect themselves and others in a reasonable and fair manner. They are obliged to ensure that transparent and honest systems preside both at home and work. This is a core obligation of competent leaders.

Finally, once the letting go is negotiated successfully and to the benefit of all concerned the path to "NEW BEGINNINGS" opens.



In conclusion, healthy and dynamic communication systems strongly support the positive management of change and transition processes. When human factors are not addressed proactively and courageously, then they have the power to sabotage or jeopardize change because seriously challenging and destructive emotions end up manipulating behaviours and reactions. Hence, successful change and transitions that involve people require competent communications that always revolve around assertiveness.

As already outlined above, in themselves these are superb strategic self care measures because they dramatically reduce personal negative pressure, stress and in the long run burnout. All other technical and academic models, tools, strategies, frameworks, guidelines and policies help to address the content and therefore enhance the result. The process, which is at the core of anything we do, remains the undisputed decisive issue.

I hope you have enjoyed this series of four letters and that they have wet your appetite for human factors in the health sector. Thank you for taking the time to read them and to reflect on your well being and self care. Whether you introduce some of the changes recommended or consider the concepts outlined in this series depends entirely on you. I obviously encourage you to do so and enjoy the benefits. Thank you and good luck!

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Clinical Reflections on He

by **Christian A Scerri** *MD PhD(Molecular Genetics)*
Clinical and Molecular Geneticist
Clinical and Molecular Genetics Clinic
Speciality Clinics, Mater Dei Hospital

To be effective and safe, the coagulation process should induce the formation of a blood clot in the right amount and at the right time. Haemostasis, is the result of interplay between damaged blood vessels, platelets and coagulation factors. The coagulation pathway is a proteolytic cascade, with each enzyme of the pathway present in the plasma as a zymogen (an inactive form), which on activation undergoes proteolytic cleavage to release the active factor from the precursor molecule. The initiation of the coagulation cascade can arise from two major pathways, the Intrinsic and Extrinsic pathways, that finally merge into one common pathway, with thrombin as its final product. Thrombin converts soluble fibrinogen to insoluble fibrin that is essential for clot formation. In similar fashion to other physiological processes, the coagulation cascade involves a number of positive and negative feedback mechanisms that ultimately produces a fine balance between thrombophilic and thrombolytic processes. Any variation in the protein structure of any of the components of the coagulation system can give rise to coagulation disorders.

Whilst the Hereditary Haemophilias (Classic Haemophilia – factor VIII deficiency – and Christmas Disease – factor IX deficiency) are serious conditions, potentially causing severe morbidity and an increase in mortality, their prevalence in the general population is relatively low. The reverse side of the coin, i.e. hereditary thrombophilias (an increased tendency for thrombosis), whilst not rare are often overlooked. The most common proteins involved in hereditary thrombophilias are Protein C, Protein S, prothrombin, Factor V and methylene tetrahydrofolate reductase.

Protein C is synthesized in the liver as an inactive protein, which circulates in the blood. Activation of the protein occurs on cell surfaces by the action of thrombin. Activated Protein C inhibits thrombin formation by inactivation of key cofactors (FVa and FVIIIa) required in procoagulant enzymatic complexes. Hereditary Protein C deficiency is inherited as an autosomal recessive condition with a prevalence of around 1 in 200 to 300. Protein S is a vitamin K–dependent anticoagulant protein which acts as a cofactor to activated protein C. Hereditary Protein S deficiency is an autosomal dominant disease. The prevalence of hereditary Protein S deficiency is estimated to be around 1 in 700.

Prothrombin (Factor II) is the thrombin precursor protein produced by the liver and, similar to the other coagulation factors, present within the plasma protein component. Prothrombin is converted into thrombin as part of the coagulation cascade and is pivotal in clot formation. Blood prothrombin levels have a direct affect on the efficiency of the coagulation process. A single point mutation in the untranslated, 3' region of the prothrombin gene (G20210A) causes elevated plasma prothrombin levels, which in turn leads to increased rates of thrombin generation, and an increase in the risk for a thrombotic event due to the potential for excessive growth of fibrin clots. The presence of this allele increases the risk of deep vein thrombosis (DVT) by 2-3 times.[1,2] It is estimated that around 2.7%[3] of the Maltese population carries this allele.

Activated Factor V (FVa), together with activated Factor X (FXa), induce the conversion of Prothrombin to Thrombin. The gene for this factor is located on chromosome 1 and is about 70Kb (kilobases) in length (approximately equal in length to the whole of the beta globin gene locus) and is made up of 25 exons. In contrast to most of the other coagulation factors, FVa acts as a cofactor and is essential for the conversion of prothrombin. It is thus also the prime site for the negative feedback mechanism that limits thrombin formation. This occurs through the inactivation of FVa by activated Protein C. Certain mutations within the Factor V gene, produce a protein that shows a resistance to Protein C degradation, with the resultant increased activity of Factor V. The most common mutation within this group is the replacement of an arginine residue with glutamine at amino acid position 506 (R506Q), commonly known as Factor V Leiden. It is estimated that the prevalence of Factor V Leiden amongst the Maltese population is of 2.3%[3] and the presence of this allele, increases the risk of DVT by 3-8 times.[1,4]

Methylenetetrahydrofolate reductase (MTHFR) is a cytoplasmic enzyme that irreversibly reduces[5],10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which in turn is used to convert homocysteine (a potentially toxic amino acid) to methionine by the enzyme methionine synthase. Two DNA sequence variants (polymorphisms) in the MTHFR gene at basepair 677 (a change from a C to a T) and at basepair 1298 (a change from an A to a C), reduce its enzymatic activity, by 50% and 34% respectively. Homozygosity of either polymorphism or compound heterozygosity increases the risk of DVT.[5]

Juvenile Venous Thromboembolism
Recurrent Venous Thromboembolism
Family history of Venous Thromboembolism
Thrombosis in unusual sites (portal or mesenteric veins, cerebral sinus)
Recurrent fetal loss
Pre-eclampsia, HELLP-syndrome
Skin necrosis induced by coumarins (deficiency of Protein C or S, prothrombin mutation)
Neonatal Purpura Fulminans (homozygous Protein C or homozygous Protein S deficiency)
Heparin resistance (severe antithrombin deficiency)

Table 1: *Clinical presentations of the various inherited thrombophilic conditions.*

ereditary Thrombophilia

Thrombophilic Status	Relative Risk of Venous Thrombosis
Normal	1
Oral contraceptive (OC) use	4
Factor V Leiden, heterozygous	5 to 7
Factor V Leiden, heterozygous + OC	30 to 35
Factor V Leiden, homozygous	80
Factor V Leiden, homozygous + OC	>100
Prothrombin Gene Mutation, heterozygous	3
Prothrombin Gene Mutation, homozygous	Also possible risk of arterial thrombosis
Prothrombin Gene Mutation, heterozygous + OC	16
Protein C deficiency, heterozygous	7
Protein C deficiency, homozygous	Severe thrombosis at birth
Protein S deficiency, heterozygous	6
Protein S deficiency, homozygous	Severe thrombosis at birth
Antithrombin deficiency, heterozygous	5
Antithrombin deficiency, homozygous	Thought to be lethal prior to birth
MTHFR Deficiency, homozygous	2 to 4
MTHFR Deficiency, homozygous combined with Factor V Leiden, heterozygous	20

Table 2: *The relative risk of venous thromobosis amongst carriers, homozygotes and heterozygotes of the various inherited thrombophilias.*

Considering the high prevalence of these variants in the Maltese population and considering the potentially serious conditions they are associated with, who should be tested and how? Though the easiest answer to this question would be a whole population screening, this cost (both of the actual tests as well as in counseling time) to benefit ratio of such an approach is high and it would result in a high degree of undue anxiety and stress to the individual being tested. A more reasonable approach would be that of targeted testing. The recommended testing protocol would include:

1. PATIENTS WITH VENOUS THROMBOEMBOLISM

- Patients with a first episode of venous thromboembolism in young patients (<50 years of age)
- Patients with a first episode of venous thromboembolism at >50 years with a positive family history for thrombotic phenomena
- Patients presenting with recurrent episodes at any age without the presence of any other predisposing condition.
- Venous thrombosis in unusual sites (such as hepatic, mesenteric and cerebral veins).

2. PATIENTS WITH ARTERIAL THROMBOSIS

- Young patients who develop acute arterial thrombosis in the absence of other traditional risk factors
- Myocardial infarction in female smokers under 50 years of age
- Female patients receiving hormonal replacement therapy
- Patients with early saphenous vein graft failure

3. ASYMPTOMATIC WOMEN

- Asymptomatic women with a positive family history for venous thromboembolism before use of oral contraceptives or hormone replacement therapy
- Women with recurrent pregnancy loss or unexplained intrauterine fetal growth retardation or stillbirth
- Women with severe pre-eclampsia

4. OTHER ASYMPTOMATIC SUBJECTS

- Asymptomatic relatives of patients with known inherited thrombophilia

Considering the relative high risk of venous thrombosis in individuals heterozygous for Factor V Leiden or heterozygous prothrombin deficiency and oral contraceptive therapy (OCT), it is arguable whether testing for these thrombophilia conditions should be carried out prior to starting OCT. It is generally considered that the cost to benefit value of screening for thrombophilia prior to OCT is low. On the other hand it is advisable to take a detailed personal and family history of deep vein thrombosis prior to the prescription of OCT or at a first antenatal visit. This should detect those individuals that are at risk of having one of the inheritable thrombophilias and in whom testing would be worthwhile.[6]

DNA tests for mutations causing inheritable thrombophilic disorders are available from the Laboratory of Molecular Genetics at the Pathology Department and requires a blood sample in an EDTA vial. Other biochemical tests are also available at the Pathology Department and require a citrated blood sample. Those individuals with a positive result should be given adequate counselling (can be referred to the Molecular Genetics Clinic, Speciality Clinics at Mater Dei Hospital) as well as proper advice (as required) regarding anticoagulant treatment, oral contraceptive and hormone replacement therapy, folic acid supplementation as well as proper hydration and exercise in cases of prolonged bed rest and long haul flights.

References

1. Koster T, Rosendaal FR, Briet E, Vandenbroucke JP. John Hageman's factor and deep-vein thrombosis: Leiden thrombophiliaStudy. *BR J Haematol 1994; 87:422-4.*
2. Tirado I, Soria JM, Mateo J et al. Association after linkage analysis indicates that homozygosity for the 46C-->T polymorphism in the F12 gene is a genetic risk factor for venous thrombosis. *Thromb Haemost* 2004; 91:899-904.
3. Abela Medici J, Bezzina Wettinger S, Scerri CA, Grochowska A, Felice AE. Comparative Frequency of Coagulation Factor II and Coagulation Factor V Alleles among New-Born and Senior Citizens. *Malta Medical Journal* 2005; 17(1):20-7.
4. Bertina RM, Reitsma PH, Rosendaal FR. Vandenbroucke JP. Resistance to activated protein C and factor V Leiden as risk factor for venious thrombosis. *Thromb Haemost* 1995; 74:449-53.
5. den HM, Koster T, Blom HJ et al. Hyperhomocysteinemia as a risk factor for deep-vein thromosis. *N Engl J Med* 1996; 334:759-62.
6. Vandenbroucke JP, van der Meer FJ, Helmerhorst FM, Rosendaal FR. Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1996; 313:1127-30.

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Dr Ethel Farrrugia receiving her eQUIZ prize.

The process of good Clinical P

Clinical Practice Guidelines (CPGs) are being developed and implemented as an integral part of medical care in the developed world. Evidence shows that there are significant improvements in care and outcomes after introduction of CPGs.[1,2] Development of CPGs for internal use by the Department of Medicine started in 2003 in St. Luke's Hospital, and is now continuing at Mater Dei Hospital.

CPGs are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".[3] The aims of CPGs are to achieve improvements in quality and appropriateness of care and to maintain cost-effectiveness. Their role is also as educational tools, helping practitioners to implement the ever-increasing amount of evidence and opinion on best current practice.

It is important to note that Guidelines are different from Protocols in that protocols are a more rigid set of rules which one has to follow very closely, leaving little space for clinical discretion. An example of a protocol would be the Cardiopulmonary resuscitation (CPR) algorithms. The terminology 'protocol' has thus limited place in everyday medical decisions, and the term 'guideline' has largely replaced it. This is because no clinical scenario can ever be exactly the same as another and thus no guideline can ever be specific enough to be applied to all situations. *Consequently, CPGs should be regarded as* ***advisory, not mandatory*** *in nature.*

Good quality guidelines are developed within **Guideline Development Groups** (GDGs), which are headed by a Chairperson.[4] In our case, this role is fulfilled by a Guideline Co-ordinator, who is a senior member of the speciality of the CPG in development. We have also introduced the role of a Guideline Developer, who is the person who draws up the guideline, based on the available evidence. Together with the Guideline Co-ordinator, he/she should keep the momentum of development going until publication. The GDG is made up of experts, stakeholders and representatives who should be able to offer help with research, advice, and direction.

As described above, it is essential that CPGs do not replace clinical judgement and they should leave space for **clinical discretion**. Inflexibile CPGs leave no room to tailor care and apart from discouraging their use, will decrease the popularity of that CPG. It is equally inadvisable to follow a guideline blindly, without keeping in mind the whole clinical picture.

CPGs need to be **specific** where evidence-based medicine permits. Sections on Quality of evidence and Strengths of recommendations should feature in the CPG to express the Level of evidence in favour of each recommendation. The clinician would then be guided as to the extent of clinical discretion he can use.

CPGs have always to be taken in a **local context**. They cannot always create standards of care mainly because

Practice Guideline development

local resources vary in different countries. Thus limited resources in a particular area might dictate the choice of a less desirable alternative in terms of a specific management strategy.

Clarity of communication is paramount for effective guidelines. We all know that most clinicians are hard pressed for time, and will not waste time to try to comprehend an unnecesserily cumbersome, lengthy and tortuous text, peppered with references. Thus for example, Algorithms are used to facilitate movement of the clinician along the CPG recommendations. In the absence of adequate clarity, the guideline will not be used by the people who are meant to use it.

In order to aid this, our CPGs are developed in two parts. The first will show the **essential outline** of the guideline, keeping it as short and simple as possible. A second part of the CPG will include further **explanatory notes and references**. This imparts credibility and reproducibility to the guideline and will be valuable when the guideline is revised and updated.

Availability and **ease of access** are the last step before the clinician can use CPGs usefully. Without these features, the best CPGs fall short of their full potential.

In conclusion, CPGs can be very useful tools for the modern clinician with electronic resources at his/her fingertips. Care must be taken to avoid some pitfalls which include cumbersome, detailed CPGs of no practical clinical use, or rigid CPGs which leave little space for clinical discretion. Following a CPG blindly, may also lead to inappropriate care. However if developed and used in a proper way, easily accessible CPGs can definitely improve quality and efficacy of care.

References:

1. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice:a sytematic review of rigorous evaluations: *Lancet* 1993; 342:1317-22.

2. Effective Health Care Bulletin. Implementing clinical practice guidelines. York:University of York, 1994.

3. Field MJ, Lohr KN. Institute of Medicine Committee to advise the Public Health Service on Clinical Practice Guidelines. Clinical Practice Guidelines: directions for a new program. Washington DC: National Academy Press; 1990.

4. Scottish Intercollegiate Guideline Network: A guideline developer's handbook; January 2008. Available at www.sign.ac.uk/pdf/sign50-2008.pdf.

Dr Tonio Piscopo MD, MRCP (UK), DTM&H is a Consultant in General Medicine and Infectious Diseases. He has been Vice-Chairman and Main Guideline Co-ordinator of the Guideline Co-ordinating Committee of the Department of Medicine since 2003. He is also Site Manager of *www.clinicalguidelines.org*

Ancient Egyptian Medicine

Part III – Medicine and Therapeutics

by **Charles Savona-Ventura** *MD DScMed FRCOG AccrCOG MRCPI*
Professor of Obstetrics & Gynaecology, Faculty of Medicine & Surgery, University of Malta

While external disease or trauma was easily identifiable and related to a particular event, ancient populations often looked at internal disease as unexplainable and correlated with the influence of malicious spirits or deities. The Ancient Egyptians were no exception and often their medical culture developed mythological concepts to help protect them from internal disease. Mention has already been made of the recourse made by parturient women to the deities Bes and Taweret. Other deities in the Ancient Egyptian pantheon were attributed with protective and healing magical powers.

In the various Egyptian medical texts, Isis is shown to have held an important place in the pantheon of healing deities. Her legend is full of episodes of magic cures, and repeatedly she appears as the great magician whose counsel is the breath of life, whose sayings drive out sickness, and whose word gives life to him whose breath is failing. Horus, son of Isis and Osiris, was the falcon-headed sky god. The mythical story of his fight with Seth, established Horus as the god of the sun and god of life and of all good. During his battle against Seth, Horus had his eye gouged out. This was later restored by the deity Thoth. The eye of Horus (the Ugiat) remained a magical talisman for health throughout Egyptian history. The British Museum Medical Papyrus written at the end of the 18th Dynasty (circa 14th century BC) records how the Ugiat was invoked while applying a remedy to diseased eyes with the following charm recited four times. "*This Eye of Horus created by the spirits of Heliopolis, which Thoth has brought from Hermopolis – from the great hall in Heliopolis, - in Pe,- in Dep, sayest thou to it: 'Welcome, thou splendid Eye of Horus, - thou content of the Eye of Horus – brought to drive out evil of the god, the evil of goddess, the demon, male and female, the dead, male and female, the enemy, male and female, who have insinuated themselves into the eyes of the sick under my fingers. – Protection, behind me protection, come protection*!" Horus had also been stung by a deadly scorpion and was saved by the powerful spells of the gods. He thus was considered to have himself acquired special facilities to cure people bitten by venomous animals. The deity Ptah-Patecus, when depicted in his alternative form as a deformed dwarf with twisted legs, hands on hips and a huge head shaved except for the childish lock, played the role of protector against noxious animals and against all kinds of evil. The ibis-headed or dog-headed ape Thoth was considered a great physician and magician acting as physician to the god Horus. He was regarded as the god of magic, and was the arbiter between the gods and had the knowledge needed by the dead to pass safely through the underworld. In the introduction to the Ebers Papyrus, it is stated that "*I* (Re, the sun god) *will save him from his enemies, and Thoth shall be his guide, he who lets writing speak and has composed books; he gives to the skilful, to the physicians who accompany him, skill to cure.*"

Recourse to the use of charms and invocations was also made as accompaniments to herbal medicine. It was expected that physical medicines, such as herbs assuaged pain; only the magical invocation affected the cure. Thus for example, the Ebers Papyrus describes several charms and invocations that were used to encourage healing. One is used before taking a herbal remedy as follows: *"Come Remedy! Come thou who expellest (evil) things in this my stomach and in these my limbs!"*; also the same text links the two perceived therapeutic options with the statement "*Magic is effective together with medicine. Medicine is effective together with magic"*. Other therapeutic options were used for various disease conditions, including massage: "*Examination of a woman aching in her legs and her calves after walking You should say of it 'it is discharges of the womb'. You should treat it with a massage of her legs and calves with mud until she is well"* [Kahun Medical Papyrus]; as well as therapeutic herbs and foods.

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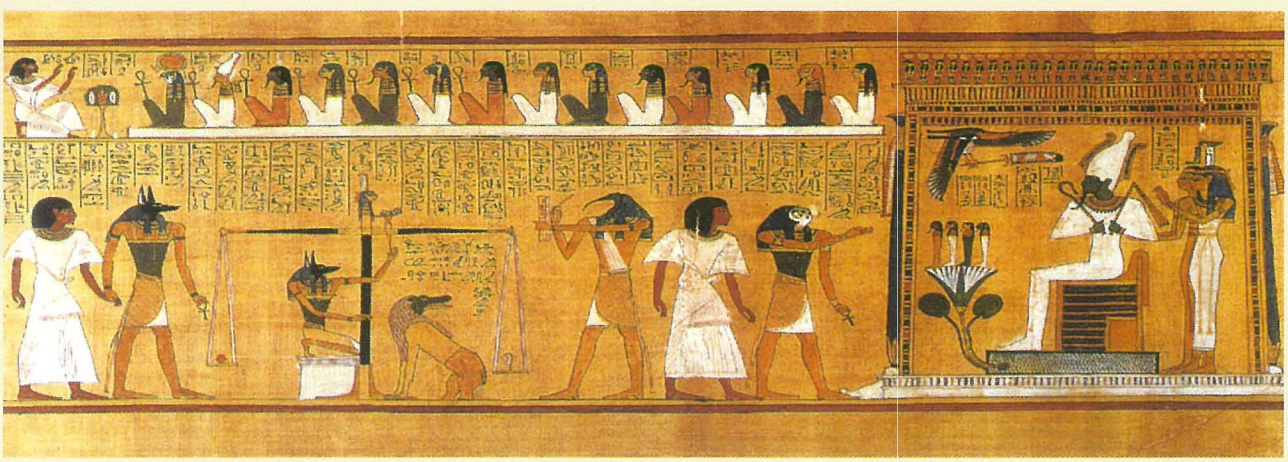

Effective relief from cold and flu symptoms.

Panadol Cold & Flu is highly effective on...

Runny Nose • Blocked Nose • Sneezing
Headache • Itchy Eyes • Fever

Dosage - Adults and children of 12 years and over:
Two caplets up to four times a day

Panadol Cold & Flu Caplets Product Information

Description:
Each tablet contains: Paracetamol 500mg
Pseudoephedrine Hydrochloride 30mg
Chlorpheniramine Maleate 2mg

Pharmacology:
Paracetamol is clinically proven analgesic and antipyretic. Pseudoephedrine is a sympathomimetic agent, for symptomatic relief from nasal congestion. Chlorpheniramine maleate is an antihistamine.

Indications:
PANADOL Cold & Flu caplets are indicated for the relief of symptoms of the common cold and influenza such as: fever, nasal congestion, sinus congestion, headache and sinus pain, sneezing, itchy and watery eyes.

Dosage and administration:
PANADOL Cold & Flu caplets are suitable for adults and children of 12 years of age and over.
Adults and children of 12 years and over: two caplets up to four times a day. If necessary the dose may be repeated every four to six hours but do not take more than four doses (8 caplets) in 24 hours.

Contraindications:
PANADOL Cold & Flu caplets are contra-indicated in patients with known hypersensitivity to paracetamol, pseudoephedrine hydrochloride or chlorpheniramine maleate or related compounds. Not to be used by patients taking monoamine oxidase inhibitor antidepressants or within two weeks of stopping such treatment.

Precautions:
Keep out of reach of children.
This preparation contains paracetamol. Do not exceed the stated dose.
Do not take other paracetamol, containing medications, nasal decongestants, or antihistamines at the same time as PANADOL Cold & Flu caplets.
PANADOL Cold & Flu caplets should be administered with caution to patients with hepatic or renal dysfunction, severe hypertension, cardiac or peripheral vascular disease, hyperthyroidism or on antihypersensitive or antidepressant therapy. Pseudoephedrine should be given with care to patients with diabetes mellitus, closed-angle glaucoma, or prostrate enlargement. Anginal pain may be precipitated in angina pectoris. Antihistamines should be used with caution in conditions such as epilepsy, prostatic enlargement, urinaryretention, glaucoma, severe cardiovascular disorders or pyloroduodenal obstruction.
Do not take this product for more than 10 days or for fever more than 3 days unless directed by a doctor. If pain persists or gets worse, if new symptoms occur, or if redness and swelling is present consult a doctor because these could be signs of serious condition. If nervousness, dizziness or insomnia occur, if a sore throat is severe and persists for more than two days and is accompanied by fever, headache, rash, nausea or vomiting, consult a doctor promptly.
Use in Pregnancy and Lactation:
Although there are no known risks associated with the use of these active ingredients during pregnancy, as with all medicines, medical advice should be sought before using this product. PANADOL Cold & Flu should not be used during breast feeding as there may be risks associated with the use of antihistamines in infants.

Use in Children:
Do not give to children below 12 of age.

Driving and Operating Machinery:
Since PANADOL Cold & Flu caplets contain an antihistamine, sedation may occur impairing the ability to drive or operate machinery.

Side Effects:
Paracetamol: When taken in recommended doses, paracetamol is usually free from side effects. However skin reactions such as urticaria have been reported rarely.
Pseudoephedrine: May occasionally cause anxiety, tremor, dizziness, cardiovascular effects including tachycardia and hypertension, insomnia reported rarely.
Chlorpheniramine: The antihistamine may cause sedation, gastrointestinal disturbances and antimuscarinic effects.

Drug Interactions:
Paracetamol: PANADOL Cold & Flu caplets may interact with anticoagulant agents on prothrombin time. The liver effects of PANADOL Cold & Flu caplets may be increased by the use of alcohol and the concomitant use of certain drugs which enhance the metabolism of paracetamol in the liver (i.e. barbiturates, tricyclic antidepressants).
Co-administration of pseudoephedrine and MAOI's may lead to hypertensive crisis. The effect may persist for up to 2 weeks after discontinuation of MAOI's.
Enhanced sedative effects of chlorpheniramine can occur with simultaneous administration of alcohol, anxiolytics and hypnotics. Tricyclic antidepressants and antimuscarinic can increase antimuscarinic side effects.

Overdosage:
In massive paracetamol over dosage, Panadol Cold & Flu caplets may cause liver damage. Early symptoms may include pallor, nausea, vomiting, (diaphoresis) and general malaise.
Clinical and laboratory evidence of liver damage may not be apparent for 48 hours to 72 hours post-ingestion. Overdose should be promptly treated by gastric lavage followed by intravenous N-acetylcysteine or methionine without waiting for the results of plasma paracetamol levels.
Additional antidote therapy is normally considered in light of further plasma paracetamol levels and the time elapsed since ingestion. In all cases of suspected overdose, prompt medical attention is critical for adults as well as for children, even if you do not notice any signs or symptoms.
Pseudoephedrine overdose is likely to result in effects similar to those listed as adverse effects, and may also produce excess sympathetic stimulation. 7-8 caplets have been shown to cause hypertension in normotensive subjects. Treatment of pseudoephedrine overdose is mainly symptomatic. Measures should be taken to support respiration and control hypertension. Convulsions should be supported with an anticonvulsant if required. Elimination of pseudoephedrine can be accelerated by acidification of the urine. Antihistamine over dosage may cause sedation and central nervous system depression.

Pharmaceutical precautions
Store below 25°C. Store in a well sealed container.

Legal Category: OTC
Market Authorisation Number: MA575/00101

For further information please contact GlaxoSmithKline (Malta) Ltd, Consumer Healthcare 13/11 Vincenti Buildings, Strait Street, Valletta. Tel: 21234044

Depression during pregnancy

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Management of mood disorders during pregnancy

The most important issue in the management of mood disorders during pregnancy is that they are actively managed. Recognition of depressive symptoms during pregnancy, in practice frequently means that although recognized, they are not treated. Antidepressant medication is indicated for severe depressions: these are unlikely to respond to talking therapies. Clinicians should discuss the possibility of pregnancy and parenthood with all women of reproductive years who have a history of mood disorder, regardless of whether they plan to have a family imminently or not. Most pregnancies are unplanned and such discussions may prevent abrupt discontinuation of medication.

The primary concerns regarding use of psychotropic medications during pregnancy and lactation include physical or neurobehavioral teratogenesis in the fetus, neonatal toxicity, and neonatal withdrawal. Of particular importance during pregnancy is that polypharmacy should be avoided if possible. Besides, medications should be titrated to the minimum effective dose.

It can be a difficult challenge to determine the correct therapeutic dose of medication during pregnancy. Pregnancy alters the pharmokinetics of psychotropic medications producing effects such as decreased gastric acid and gastrointestinal emptying,[15] increased extracellular fluid volume and body fat, changes in intrahepatic (P450 system) and extrahepatic activity[16] and increased glomerular filtration rate and renal blood flow.[17] Due to these pharmacokinetics changes, clinicians should closely monitor patients, particularly during the third trimester and the postpartum to ensure adequate dosing of medications.

Amitriptylene and imipramine are the recommended drugs of choice for the treatment of depression during pregnancy, based on the length of time that they have been in use and the cumulative data on their lack of foetotoxicity. However in reality, SSRIs are frequently prescribed during pregnancy as they are the drugs of choice for most psychiatrists and family doctors outside of pregnancy and there is cumulative positive evidence about safety to the foetus. Fluoxetine has been extensively studied in pregnancy and data showed no increase in either the incidence of malformations or spontaneous abortions.[18] Although there are less reprotoxicology data available on citalopram, fluvoxamine and sertraline there is no clear evidence of an increased risk of foetal toxicity or other pregnancy complications so far.[18,19] Neonatal withdrawal symptoms may occur following chronic use of any antidepressant or their use near the time of delivery. Therefore if clinically appropriate, the dose of the antidepressant should be tapered 3-4 weeks prior to the expected date of delivery to minimize withdrawal symptoms.

References

1. Glover V. Maternal stress or anxiety in pregnancy and emotional development of the child. British Journal of Psychiatry 1997; 171:105-6.

2. Kumar R, Robson KM. A prospective study of emotional disorders in childbearing women. *British Journal of Psychiatry* 1984; 144:35-47.

3. O'Hara MW, Swain AM. Rates and risks of postpartum depression - a meta-analysis. *International Review of Psychiatry* 1996; 8:37-54.

4. Scholle SH, Haskett RF, Hanusa BH, Pincus HA, Kupfer DJ. Addressing depression in obstetrics/gynaecology practice. *Gen Hosp Psychiatry* 2003; 25(2):83-90.

5. Nonacs R, Cohen LS. Depression during pregnancy: diagnosis and treatment options. *J Clin Psychiatry* 2002; 63(7):24-30.

6. Evans J, Heron J, Francomb H, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. *BMJ* 2001; 323(7307):257-60.

7. Josefsson A, Angelsiöö L, Berg G et al. Obstetric, somatic, and demographic risk factors for postpartum depressive symptoms. *Obstet Gynecol* 2002; 99:223–8.

8. Gotlib I, Whiffen V, Mopunt J, Milne K, Cordy K. Prevalence rates and demographic characteristics associated with depression and the postpartum. *Journal of Consulting and Clinical Psychology* 1989; 57:269-74.

9. Kitamura T, Sugawara M, Sugawara K, Toda MA, Shima S. Psychosocial study of depression in early pregnancy. *The British Journal of Psychiatry* 1996; 168:732-8.

10. Zuckermann B, Amaro H, Cabral H. Depressive symptoms during pregnancy: relationship to poor health behaviours. *American Journal of Obstetrics and Gynaecology* 1989; 160:1107-11.

11. Lou HCD, Nordenfolt M et al. Prenatal stresses of human life affect fetal brain development. *Development Medicine and child Neurology* 1994; 34:826-32.

12. Teixeira JM, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. *BMJ* 1999; 318:153-7.

13. Glover V. Maternal stress or anxiety in pregnancy and emotional development of the child. *British Journal of Psychiatry* 1997; 171:105-6.

14. Marcus SM. Flynn HA, Blow FC, Berry KL. Depressive symptoms among pregnant women screened in obstetric settings. *J Omens Health* (Larchmont) 2003: 29-33.

15. Ward RK, Zamorski MA. Benefits and risks of psychiatric medications during pregnancy. Am Fam Physician 2002; 66:629–36.

16. Robson, SC Mutch E, Boy RJ et al. Apparent liver blood flow during pregnancy: A serial study using indicyanine green clearance. *Br J Obstet Gynaecol* 1990; 97:720–4.

17. Davison JM, Hytten FE. Glomerular filtration during and after pregnancy. *Br J Obstet Gynaecol* 1974; 81:588–95.

18. Addis A, Koren G. Safety of fluoxetine during the first trimester of pregnancy: *A meta analytic review of epidemiological studies Psychol Med* 2000 30:89-94.

19. Sanz E, De-las-Cuevas C, Kiuru A, Bate A, Edwards R. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: *a database analysis, Lancet* 2005; 365:482-7.

TREATING YOUR POST-MENOPAUSAL OSTEOPOROSIS PATIENTS

FOSAVANCE™ Tablets
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are a logical progression

- Reduces the risk of hip and vertebral fractures[1]
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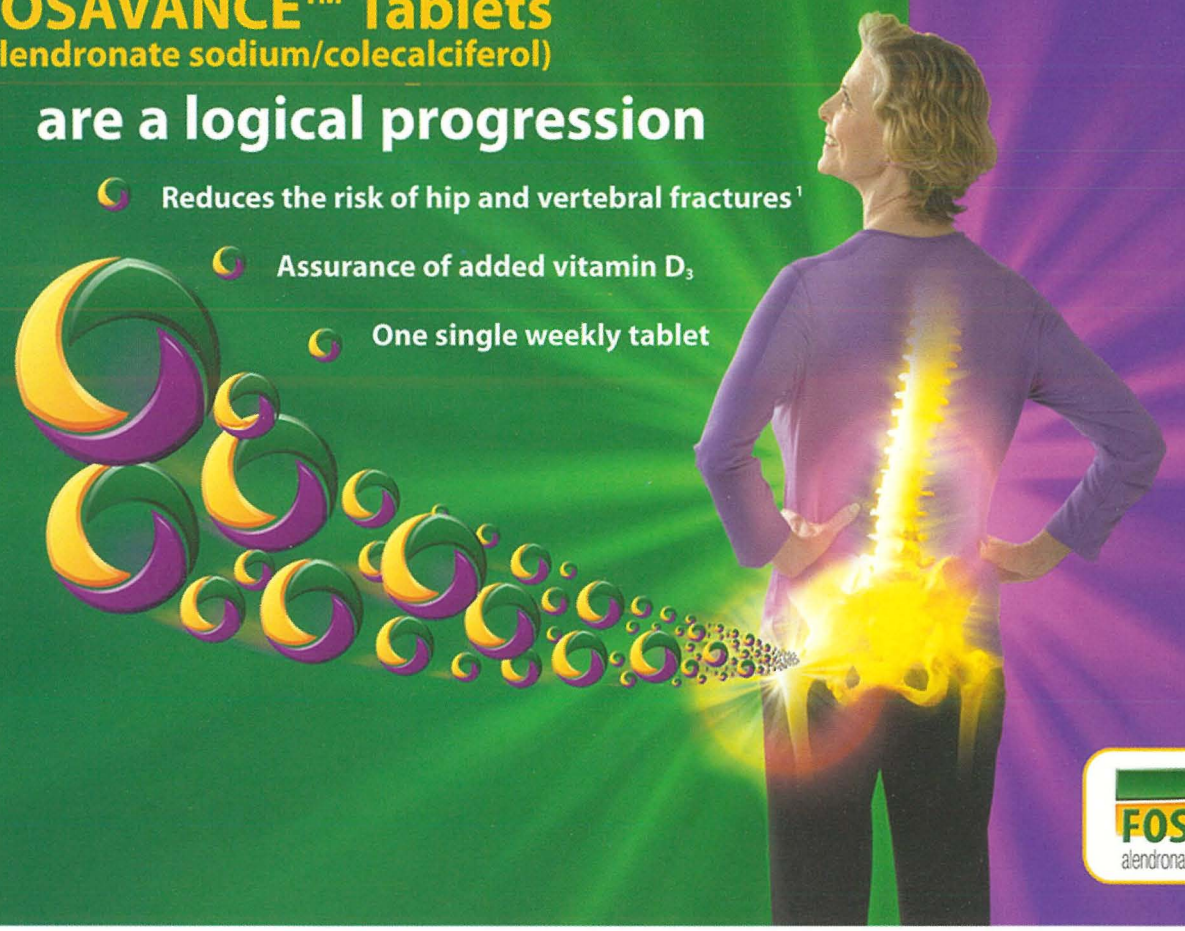

FOSAVANCE™
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FOSAVANCE™ Tablets (70 mg Alendronic Acid as Alendronate Sodium Trihydrate and 70 micrograms [2,800 IU] Colecalciferol [vitamin D_3])

ABRIDGED PRODUCT INFORMATION
Refer to Summary of Product Characteristics before prescribing.

PRESENTATION
Capsule-shaped, white to off-white tablets marked with an outline of a bone image on one side, and '710' on the other, containing 70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2,800 IU) colecalciferol (vitamin D_3).

USES
Treatment of post-menopausal osteoporosis in patients at risk of vitamin D insufficiency. 'Fosavance' reduces the risk of vertebral and hip fractures.

DOSAGE AND ADMINISTRATION
The recommended dosage is one (70 mg/ 70 microgram) tablet **once weekly.**
Patients must be advised to follow the instructions below:
For adequate absorption of alendronate: Take at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate. *The following instructions should be followed exactly in order to minimise the risk of oesophageal irritation and related reactions:*
- Swallow 'Fosavance' only upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Do not chew the tablet or allow the tablet to dissolve in the mouth because of a potential for oropharyngeal ulceration.
- Do not lie down until after the first food of the day which should be at least 30 minutes after taking the tablet.
- Do not lie down for at least 30 minutes after taking 'Fosavance'.
- Do not take at bedtime or before rising for the day.

Patients should receive supplemental calcium if intake is inadequate. Additional supplementation with vitamin D should be considered on an individual basis taking into account vitamin D intake from vitamins and dietary supplements. Equivalence of 2,800 IU of vitamin D_3 weekly in 'Fosavance' to daily dosing of vitamin D 400 IU has not been studied. *Use in the elderly:* No dosage adjustment is necessary. *Use in renal impairment:* No dosage adjustment is necessary for patients where GFR is greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is <35 ml/min. *Use in children:* Not recommended.

CONTRA-INDICATIONS
Oesophageal abnormalities and other factors which delay oesophageal emptying, such as stricture or achalasia. Inability to stand or sit upright for at least 30 minutes. Hypersensitivity to alendronate or to any of the excipients. Hypocalcaemia.

PRECAUTIONS
Alendronate can cause local irritation of the upper gastro-intestinal mucosa and potentially worsen any underlying disease. Use with caution in patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, or ulcers, or with a recent history (within the previous year) of gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty. Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should be alert to any signs or symptoms of a possible oesophageal reaction, and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or new or worsening heartburn. The risk of severe oesophageal adverse reactions appear to be greater in patients who fail to take alendronate properly and/or continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. While no increased risk was observed in extensive clinical trials with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe with complications. A causal relationship cannot be ruled out. Bone, joint and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and or incapacitating. From start of treatment, onset of symptoms varied from one day to several months. A subset had recurrence of symptoms when rechallenged. Patients should be instructed that if they miss a dose of 'Fosavance' , they should take one tablet on the morning after they remember. They should not take two tablets on the same day, but should return to taking one tablet once a week, as originally scheduled on their chosen day. Cause of osteoporosis other than oestrogen deficiency and ageing should be considered. Correct hypocalcaemia before initiating therapy. Other disturbances of mineral metabolism should also be effectively treated. The content of vitamin D in 'Fosavance' is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with 'Fosavance'. *Colecalciferol:* Monitor urine and serum calcium in patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis) as vitamin D_3 may increase the magnitude of hypercalcaemia and/or hypercalciuria. Patients with malabsorption may not adequately absorb vitamin D_3. *Excipients:* Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take 'Fosavance' because it contains lactose and sucrose. *Drug interactions* Food, beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products may interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking 'Fosavance' before taking any other medicinal product. *Use in pregnancy and lactation:* alendronate has not been studied in pregnant or breast-feeding women and should not be given to them.

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SIDE EFFECTS
The following adverse experiences have been reported during clinical studies and/or post-marketing use of alendronate. No new adverse reactions have been identified for 'Fosavance'. *Common (≥1.0% and <10%) Gastro-intestinal:* abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distension, acid regurgitation. *Musculoskeletal:* musculoskeletal (bone, muscle or joint) pain. *Neurological:* headache. *Uncommon (≥0.1% and <1%) Gastro-intestinal:* nausea, melaena, vomiting, gastritis, oesophagitis, oesophageal erosions. *Skin:* rash, pruritus, erythema. *Rare (≥0.01% and <0.1%) Body as a whole:* hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute-phase response. Symptomatic hypocalcaemia, often in association with predisposing conditions (see 'Precautions'). *Gastro-intestinal:* oesophageal stricture, oropharyngeal ulceration, upper gastro-intestinal PUBs (perforation, ulcers, bleeding) (see 'Precautions') localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing. *Skin:* rash with photosensitivity. *Special senses:* uveitis, scleritis, episcleritis. Isolated cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. *Laboratory test findings* In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

PACKAGE QUANTITIES AND BASIC NHS COST
'Fosavance' Tablets £22.80 for 4 tablets.

POM Date of review: September 2005

Marketing Authorisation Numbers:
'Fosavance' Tablets EU/1/05/310/02

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
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REFERENCES
1. Black DM, Thompson DE, Bauer DC et al. Fracture risk reduction with alendronate in women with osteoporosis : the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;85(11):4118-4124.

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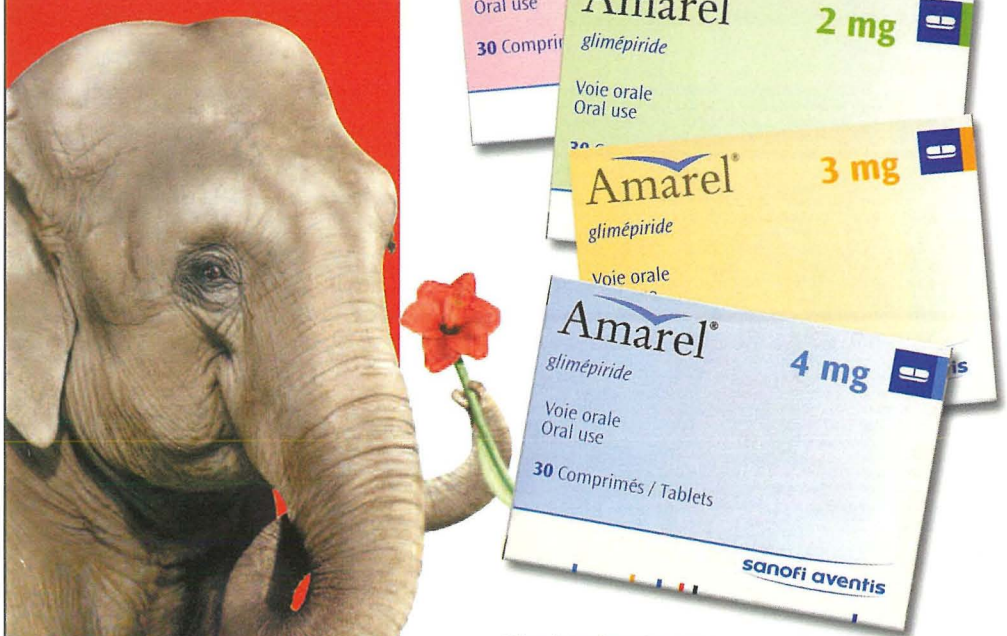

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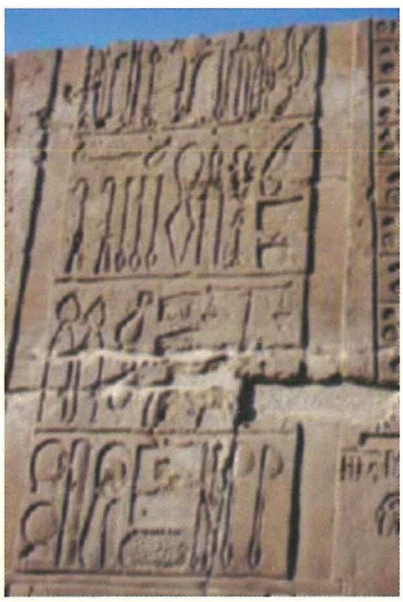
PRESCRIBING INFORMATION **Amarel® 1.0, Amarel® 2.0, Amarel® 3.0, Amarel® 4.0**. *Glimepiride* - **Composition:** Active constituent: Glimepiride Excipients: Lactose monohydrate, sodium starch glycollate, polyvidone 25000, cellulose microcrystalline, magnesium stearate Additionally the following excipients per strength: • Amarel 1 mg Iron oxide (red), E 172 • Amarel 2 mg Iron oxide (yellow), E 172, Indigotine, E 132 • Amarel 3 mg Iron oxide (yellow), E 172 • Amarel 4 mg Indigotine, E 132 **Pharmaceutical form**: Tablets Quantity in active substance: Each tablet contains 1 mg or 2 mg or 3 mg or 4mg glimepiride. **Pharmacotherapeutic category**: Antidiabetic **General information**: Amarel contains glimepiride. It is an orally active hypoglycaemic substance that belongs to the group of sulphonylureas. **Therapeutic Indications**: Amarel is indicated for the treatment of type II diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate. **Posology and Method of Administration** The dosage is based on the results of metabolic examination (blood and urinary glucose determinations). The starting dose is 1mg glimepiride per day. In case of a good regulation this dosage can be taken for maintenance therapy. In case of unsatisfactory regulation the dosage has to be increased based on the metabolic situation, stepwise with an interval of about 1-2 week between each step to 2, 3, 4 glimepiride per day. A dosage of more than 4mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6mg glimepiride per day. In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision. In patients not adequately controlled with the maximum daily dose of Amarel, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision. Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or, if none is taken - shortly before or during the first main meal. If a dose is forgotten, this should not be corrected by increasing the next dose. Tablets should be swallowed whole with some liquid. If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone. In the course of treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycaemia timely dose reduction or cessation of therapy must therefore be considered. Change in dosage may also be necessary, if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo-or hyperglycaemia. **Switch over from other oral hypoglycaemic agents to Amarel** A switch over from other oral hypoglycaemic agents to Amarel can generally be done. For the switch over to Amarel the strength and the half-life of the previous medication has to be taken into account. In some cases, especially in antidiabetics with a long half-life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect. The recommended starting dose is 1 mg glimepiride per day. Based on the response the glimepiride dosage may be increased stepwise, as indicated earlier. **Switch over from Insulin to Amarel** In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to Amarel may be indicated. The changeover should be undertaken under close medical supervision. **Contraindications:** Amarel should not be taken in the following cases • under coma or ketoacidosis status. • insulin dependent diabetes, severe renal or hepatic function disorders. • hypersensitivity to glimepiride, other sulphonylureas or sulphonamides or excipients in the tabs • pregnancy and lactation. In case of severe renal or hepatic function disorders, a change over to insulin is required. **Special precautions and warnings for use:** Amarel has to be taken shortly before or during a meal. In case of meals at irregular intervals, especially skipped meals, treatment with Amarel may lead to hypoglycaemia. The possible symptoms of hypoglycaemia include (e.g. headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia.In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias. The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke. The symptoms nearly always subside by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect. It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.In case of severe hypoglycaemia or over a protracted period, only temporarily controlled by the usual amounts of sugar, immediate medical treatment and occasionally hospitalization is required. Factors favouring hypoglycaemia include: • unwillingness or (more commonly in older patients) incapacity of the patient to cooperate, • undernutrition, irregular mealtimes or missed meals or periods of fasting, • alterations in diet, • imbalance between physicial exertion and carbohydrate intake, • consumption of alcohol, especially in combination with skipped meals, • impaired renal function, • serious liver dysfunction, • overdosage with Amarel, • certain uncompensated disorders of5th undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicines should only be taken with the knowledge (or at the prescription) of the doctor. Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g fluconazole). Results from in vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors. Based on the experience with Amarel and with other sulphonylureas the following interactions have to be mentioned. Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example: phenylbutazone, azapropazon and oxyfenbutazone.sulphinpyrazone, insulin and oral antidiabetic products, certain long acting sulphonamides, metformin, tetracyclines, salicylates and p amino salicylic acid, MAO-inhibitors, anabolic steroids and male sex hormones, quinolone antibiotics, chloramphenicol, probenecid, coumarin anticoagulants, miconazol, fenfluramine, pentoxifylline (high dose parenteral), fibrates, tritoqualine, ACE inhibitors, fluconazole, fluoxetine, allopurinol, sympatholytics, cyclo-, tro- and iphosphamides, Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: oestrogens and progestagens, saluretics, thiazide diuretics, thyroid stimulating agents, glucocorticoids, phenothiazine derivatives, chlorpromazine, adrenaline and sympathicomimetics, nicotinic acid (high dosages) and nicotinic acid derivatives, laxatives (long-term use), phenytoin, diazoxide, glucagon, barbiturates and rifampicin, acetozolamide. H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect. Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion. Glimepiride may either potentiate or weaken the effects of coumarin derivatives. Based on the metabolic reaction the glimepiride dosage may be increased stepwise, as indicated earlier. **Overdose - Treatment:** After ingestion of an overdosage hypoglycaemia may occur, that may last 12 to 72 hours and that may recur after recovery. The symptoms may not occur till 24 hours after ingestion. In general observation in a hospital is therefore recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like unrest, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions. Treatment primarily consists of preventing that glimepiride is absorbed by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbant) and sodium-sulphate (laxative). In case large quantities have been ingested, gastric lavage is indicated, leaving activated charcoal to be used afterwards and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start as soon as possible with the administration of glucose, if required first 50ml of a 50% solution intravenous as bolus, followed by infusion of a 10% solution under strict control of blood glucose. Further symptomatic treatment. In particular when treating hypoglycaemia due to accidental intake of Amarel in infants and young children, the dose of glucose given must be carefully adjusted in view of the possibility of producing dangerous hyperglycaemia, and must be controlled by close monitoring of blood glucose. **Undesirable Effects:** Based on experience with Amarel and with other sulphonylureas the following side effects have to be mentioned. • *Immune system disorders*: In very rare cases mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis is possible in very rare cases. Cross allergenicity with sulphonylureas, sulphonamides or derivatives is possible. • *Blood and lymphatic system disorders*: Changes in haematology are rare during Amarel treatment. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anemia and pancytopenia may occur. These are in general reversible upon discontinuation of medication. • *Metabolism and nutrition disorders*: In rare cases hypoglycaemic reactions have been observed after administration of Amarel. These reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, like for every diabetes therapy with medicines, on individual factors such as dietary habits and the dosage (see further under "Special warnings and special precautions for use"). • *Eye disorders*: Transient visual disturbances may occur especially at the commencement of treatment, due to changes in blood glucose levels • *Gastrointestinal disorders*: Gastrointestinal complaints like nausea, vomiting and diarrhoea, pressure or a feeling of fullness in the stomach and abdominal pain are very rare and seldom lead to discontinuation of therapy. • *Hepato-biliary disorders*: Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure. • *Skin and subcutaneous tissue disorders*: Hypersensitivity reactions of the skin may occur as itching, rash and urticaria. In very rare cases hypersensitivity to light may occur • *Investigations*: In very rare cases, a decrease in the sodium serum concentrations may occur. **Expiry date of the product:** It should be stated on the outer and inner package. Do not use it after the expiry date shown. **Special precautions for the storage of the product:** Amarel must not be stored above 25 °C. In order to be protected from moisture, it should be stored in the original package. **MODE OF SUPPLY** This medicine is subject to a medical prescription. **Holder of Marketing Authorization:** **Sanofi-aventis Malta,** Triq Kan. K. Pirotta, B'Kara BKR 1114. Tel 21493022 **MA No.** 082/00201-4

Ancient Egyptian Medicine

Part III – Medicine and Therapeutics

continued from page 16

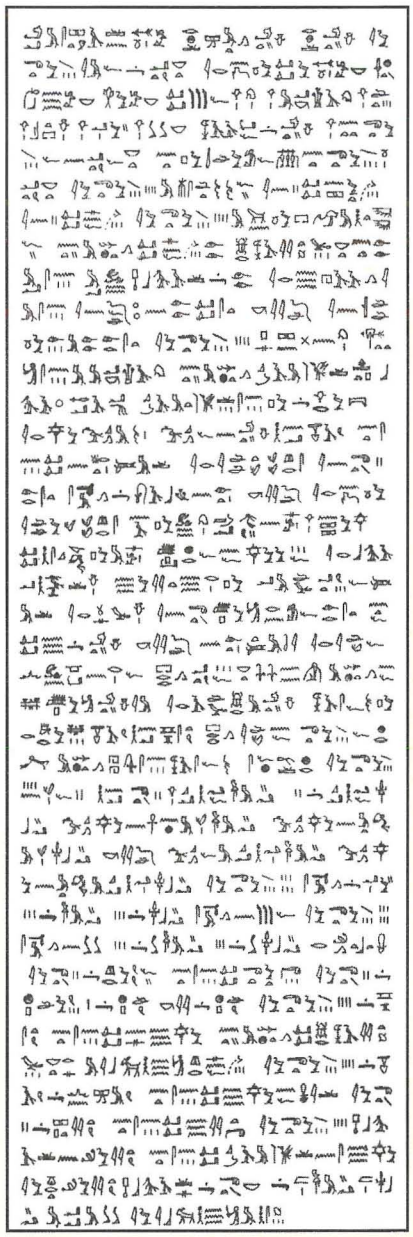
Herbs played a major part in Egyptian medicine. Examples of prescriptions can be found in the Ebers Papyrus which mentions the use of opium, cannabis, myrrh, frankincense, fennel, cassia, senna, thyme, henna, juniper, aloe, linseed and castor oil. "*For the evacuation of the belly: Cow's milk, 1; .grains, 1; honey 1; mash, sift, cook; take in four portions... To remedy the bowels: Melilot (?), 1; dates, 1; cook in oil; anoint sick part... To refresh an aching head: Flour, 1; incense, 1; wood of wa, 1; waneb plant, 1; mint (?), 1; horn of a stag, 1; sycamore (?) seeds, 1; seeds of [(?)], 1; mason's plaster (?), 1; seeds of zart, 1; water, 1; mash, apply to the head... To renew bowel movements in a constipated child: An old book, boil in oil, apply half on the belly to re-establish evacuation*" [Ebers Papyrus]. Egyptians thought garlic and onions aided endurance, and consumed large quantities of them. Cloves of garlic have been found in Egyptian burial sites, including the tomb of Tutankhamen and in the sacred underground temple of the bulls at Saqqara. Leaves from many plants, such as willow, sycamore, acacia or the ym-tree, were used in poultices and the like. Tannic acid derived from acacia nuts commonly helped to heal burns. Tape worms, "*the snakes in the belly*," were dealt with by an infusion of pomegranate root in water, which was strained and drunk. Animal products and

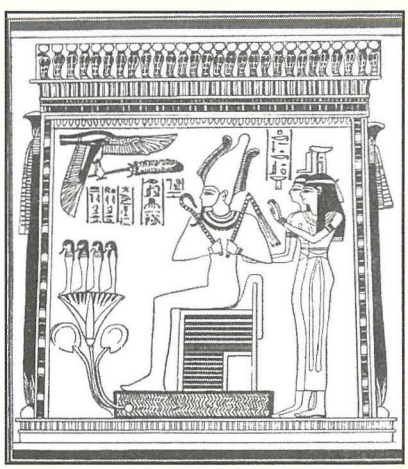


minerals were also used as pharmacological agents. Honey and grease formed part of many wound treatments; mother's milk was occasionally given against viral diseases like the common cold; fresh meat was laid on open wounds and sprains; and animal dung was thought to be effective at times. A cosmetics jar at the Cairo Museum bears the legend: "*Eye lotion to be dispersed, good for eyesight.*"

According to Herodotus there was a high degree of specialisation among physicians: "*The practice of medicine is very specialized among them. Each physician treats just one disease. The country is full of physicians, some treat the eye, some the teeth, some of what belongs to the abdomen, and others internal diseases*" [Herodotus, Histories 2,84]. Nothing certain is known about how physicians acquired their medical knowledge. It is probable that they were apprenticed to practising healers. Although the field was mainly dominated by men, we do find records of female physicians. An Old Kingdom female physician named Peseshet left a stele which recorded her positions of Overseer of Funerary Priestesses and of Overseer of Female Physicians.

Besides the medical conditions mentioned in the various medical papyri, evidence of disease states affecting the Ancient Egyptians is also furnished by the archaeological record.





Dedicated to Children

by **Marika Azzopardi**

Working with neonates, adolescents and any other age in between, Consultant Paediatric Neurologist Dr Doriette Soler comes across as a very down-to-earth woman. With a penchant for playing tennis, collecting and listening to world music especially of the South American genre, as well as enjoying micro-light flying with her better half in what has to be rigorously fine weather, she speaks about her busy workload in a professional specialization that has seen her active since 1996.

"Working with children, whether locally or overseas is always a privilege." These are her opening comments to describe a specialization that sees her treating 300 new cases presenting neurological problems per year.

"The commonest reasons for referral are seizures, movement disorders and developmental problems. Quite frankly, I have always been fascinated in knowing how the brain functions, in what makes us human and what accounts for our individuality."

Student days spent working at Id-Dar Tal-Providenza on a voluntary basis, helped her make the ultimate career decision. Taking up both local and overseas training, she moved from her initial preference in behavioural and developmental sciences to take up a specific focus in paediatric neurology, with particular emphasis on epilepsy.

Today, she is active within the International League Against Epilepsy (ILAE), holding the post of Vice President of the Malta chapter. She explains more about this,"The ILAE is an international association of physicians and other health professionals working in the field of epilepsy. The main aims are to advance and disseminate knowledge about epilepsy, to promote research, education and training and improve services and care for patients, especially by prevention, diagnosis and treatment. The chapter works closely with the Caritas Malta Epilepsy Association which was set up by voluntary workers in 1996 and now lists almost 300 members. The Association is for persons with Epilepsy and their families. I have been actively involved in the *Out of the Shadows Global Campaign Against Epilepsy* which was established in 1997 as a joint project by the WHO, ILAE and IBE (International Bureau for Epilepsy)."

Dr Soler has also been involved in a number of clinical research projects both locally and with international collaborators. Some of these projects have contributed towards improving the quality of life of children and families with epilepsy, honing in on the genetics of epilepsy, drug use in children with epilepsy and epidemiology of epilepsy. She attended a number of international epilepsy and neurological meetings and has been invited as speaker and as a trainer in paediatric neurology training courses both locally and overseas."I am a member of the British Paediatric Association, the European Paediatric Neurology Society, the Association for Research in Infant and Child Development, EUREPA (European Epilepsy Academy) and a reviewer of a number of overseas and local medical journals."

Asked about the way that working with children effects her, she comments,"From my experience in working with families both in Malta and those from other countries, I feel that what I call the ' human condition' is much the same everywhere. The advantage of working with local families is that one can understand the local customs, beliefs and culture. This is important in the field of Neurodisability where it is vital that the needs of the child within the family context are addressed."

Ultimately however, parental anxiety, hopes and concerns about their child's future are a universal reality and Dr Soler believes these to be always a major issue when one counsels parents, no matter what the family's background is.

But how easy is it to remain emotionally detached?"As a paediatrician and as a parent one cannot completely emotionally dissociate oneself from the anxiety and worries parents face when their child is diagnosed as having a serious illness or disability. Giving bad news to parents is not an easy task and needs to be done well. The professional approach essentially needs to be one which is empathic, supportive and which allows for an open discussion with parents and carers while giving a realistic picture. This requires skill and experience and loads of humanity."

Neurological conditions facing a paediatric neurologist are various , some of which are rare. She explains further,"Around one third of the workload of a general paediatrician (i.e. excluding sub specialty services) is spent managing acute or chronic neurological disease in childhood. Among the most common disorders affecting children are epilepsy, cerebral palsy, brain tumors and muscular dystrophies."

Whilst neurological problems vary in severity, some can be life-threatening while others are treatable. Most are complex problems and require a multidisciplinary approach to management. Dr Soler explains that one of the clinician's main concerns when managing children with neurodisabilities is that often parents search for a remedy and embark on the use of expensive peripheral therapies which have no scientific backing for their effectiveness.

Today, she feels that much has been done in the field of Neurology and Neurodisability in terms of health, educational and social services."The National Commission Persons with Disability has worked hard and should be applauded for the relentless efforts it has made to raise awareness on issues related to persons with disability and their families." She says that presently there is the need to address and develop expertise in specific neurological disorders and encourage more work in multidisciplinary teams. Dr Soler refers to the pressing need of giving research its due importance and in this regard incentives and funding need to be forthcoming.

"In terms of services, there is a need to consolidate the transitional care of adolescence with chronic neurological conditions when these are transferred from paediatric to adult services. There is

also a need for more small residential facilities for the care of adolescence with developmental and neurodisabilities, once they reach school-leaving age. The future of a son or daughter with a neurodisability is always the major concern of aging parents."

What about drug use? I ask Dr Soler whether she is involved in prevention or treatment of young drug abusers, or whether she can give an insight into the phenomenon vis a vis younger users?

"I am not directly involved in this field but as a clinician I have encountered a number of cases. However, I can speak as a parent. Obviously, all parents are concerned with this ever increasing phenomenon especially the ease and accessibility to alcohol. Drug abuse is a complex problem resulting from a complex interaction of a number of biological and environmental factors. As parents, I feel that the best protection we can give our children is by educating them on drug abuse, enhancing their resilience in times of stress and sharing time with them. Having realistic expectations in terms of educational achievement and developing the child's talents whatever these may be, can help children keep out of harm's way." ◻

Update on Avian Influenza

by Tanya Melillo Fenech *MD MSc(HSM) Dip(HSM)*
Public Health Physician, Disease Surveillance Unit, Department of Public Health

Human Infections with Avian Influenza A (H5N1) Viruses

2007 has ended but despite little news in the media, the avian virus is still circulating and causing deaths to wild birds, poultry and humans. In 2007 there were 85 human cases with 57 deaths (a case fatality rate of 67%). Since October 2007 there have been 23 human avian cases with 13 cases occurring in December. Indonesia is still having large number of outbreaks.

30 countries reported H5N1 cases in birds.The countries involved in poultry/birds infected with avian virus since October are Vietnam, Bangladesh, Indonesia, Myanmar, UK, Saudi Arabia, Pakistan, Romania, Poland, Egypt, Benin, Russia, Portugal and Germany.

Seasonality of Outbreaks

The H5N1 outbreaks seem to follow a seasonal pattern in line with evidence that cooler temperatures are more favourable to influenza viruses.

Human to Human Transmission

A single human to human transmission of H5N1 avian influenza virus has been confirmed by WHO in a family in Pakistan due to close contact in a very circumscribed area. It has not been possible to exclude that another transmission occurred this way also in China. It appears to be restricted though to blood relatives, suggesting that innate genetic susceptibility is the main predisposing factor.

Ground Breaking Test

LUMINEX Corporation in Toronto, have developed XTAG RVP, a ground breaking test that with a single patient sample, one can assess the presence or absence of 12 viruses that are responsible for 85% of all respiratory viral infections within a few hours.

It can test for Influenza A, A-H1, A-H3, B, Adenoviruses, RSV A and B (most common cause of bronchiolitis and pneumonia in children), Metapneumo virus (a recently diagnosed virus that causes influenza -like symptoms and is the second leading cause of respiratory infections in children), Parainfluenza 1,2,3 (which causes upper and lower respiratory infections) and Rhinoviruses(common cold).

New Influenza Vaccine

A new vaccine ACUMFLU-A manufactured by Acambis in the UK is being considered a super vaccine that beats all forms of influenza and is 90% effective. Two injections could give long lasting immunity. Two other vaccine companies, in the UK and in Switzerland are also working on an universal vaccine against all influenza viruses.

Latest studies published in Journals.

International journal *Vaccine* published a study done by Novartis on their adjuvanted influenza vaccine (FluadÆ) that showed sustained protection against seasonal influenza in the elderly population by showing a significant reduction in hospitalisation due to major conditions like pneumonia, acute coronary syndrome and cerebrovascular accidents during the influenza season.

A report in the *BMJ* following a review of over 51 publications on the effect of simple physical means on preventing respiratory infections concluded that handwashing and wearing masks, gloves and gowns are effective in preventing the spread of viruses.

Another study in the *Journal of Emerging Infectious Diseases* found that ordinary seasonal influenza vaccines may provide some protection against avian influenza. Some immune cells called CD4T-cells recognise and act against H5N1 virus and seasonal vaccine administration enhances the frequency of such reactive CD4 T-cells.

Elderberry

Black elderberry has been used as a natural remedy for common ailments like colds and coughs for centuries but recent research has pinpointed an active element called Antivirin which combats the influenza virus. Antivirin is found in the protein of the black elderberry and disarms the influenza virus by preventing it form invading healthy cells' membranes.

Pneumococcal Vaccine

Experts in the US working on pandemic preparedness are recommending that the general public take the pneumonia vaccine. This vaccine has the ability to prevent the lethal secondary bacterial infections which develop as a complication to the influenza.

Levels of Seasonal Influenza Activity

Since sentinel monitoring of influenza activity started in September 2007, in 27 countries, the level of influenza activity has so far remained low across Europe in most countries. Overall for Europe the majority of influenza viruses seen in 2007 were Influenza type A subtype H1. ◻

In-Vitro Fertilization

by **Pierre Mallia** *MD MPhil PhD MRCP FRCGP*
Associate Professor in Bioethics and Family Medicine,
Department of Family Medicine, Medical School
University of Malta

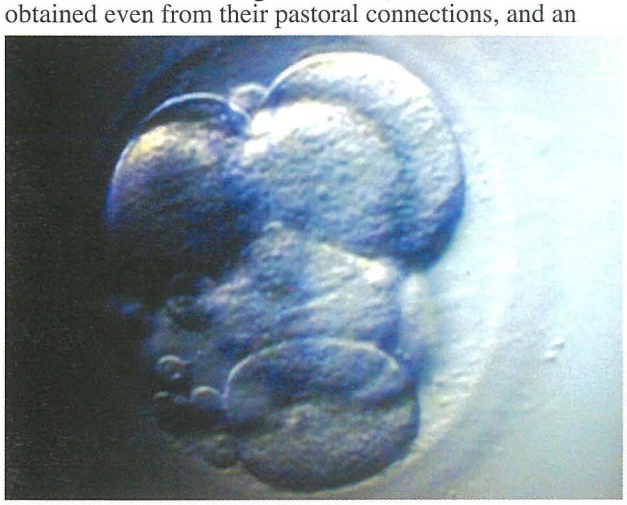
After so much debate over the last couple of years on IVF, one cannot say the final word has been said. We have certainly driven ourselves into a cul de sac especially when authorities made relevant statements effectively halting the debate. Yet parliament still has an obligation to regulate a technology, which has been introduced into the country. Shying away certainly does no good; neither does deviating arguments only to issues on the status of the embryo.

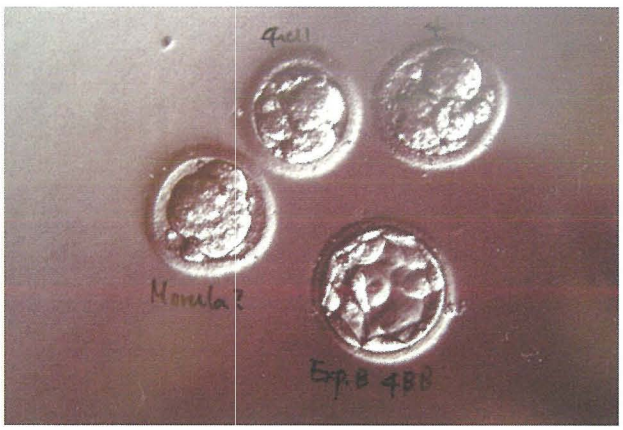
Admittedly, the failure of discussions on IVF have centred mostly around concerns for the embryo. One columnist asserted it was about 'embryocide', making allegations that we are not being charitable to the truth. Whilst embryocide is certainly a concern, it is not the main issue in IVF. Embryocide, if it occurs, can be stopped. The main problem is a conflicting issue between a morality of a cherished institution and the decision-making responsibility of our parliamentarians, who unfortunately did not engage in a fruitful discussion on *how* to legislate, other than a report made by the Parliamentary Committee for Social Affairs.

The main concerns on IVF are that the Roman Catholic Church officially considers this technology as illicit. It is illicit not because of killing of embryos but because the natural conjugal act of the couple is separated from procreation and it involves the manual stimulation of the male. The second problem which no one seemed to address is the second article in the Constitution establishing this Religion as the official religion; are there any constitutional implications towards effective legislation in this area?

Certainly the Church's position is not likely to change in the future. Yet many within the Church assert that since the technology is locally available, it should be regulated, with legitimate couples being able to decide whether to avail themselves of this technology or not.

Certainly the use of IVF by couples has to be seen within the light of an existent relationship; hopefully, no one will go through the expense involved without commitment to each other. It may not be within the normative values of the country to offer it to anyone else – singles, for example. Yet it is certainly a right of couples to make their own ethical decision with regards to IVF, based on counsel obtained even from their pastoral connections, and an





obligation on the part of the state to regulate what has been going on for years.

Many see IVF as a good in itself. This should not be overseen. It has given many couples satisfaction. The government may, due to a variety of reasons, not decide to offer this on a national health service. But the fact that it allows private hospitals to make use of this technology shows it acknowledges its value. It cannot therefore shy away from legislating to regulate, and indeed protect the embryo from actions it deems immoral. To this effect, even the Catholic Church, while arguing for the illicitness of IVF in *Donum Vitae*, at the same time guides governments to regulate IVF according to sound principles to protect life, where this is existent. Conversely, the Bioethics Consultative Committee, after producing a document on the issue, and bringing the debate to the hands of the Parliamentary Committee for Social Affairs has certainly done more than its fair share.

Although it is noble for married couples who turn up to be infertile to accept their condition and not have children, this certainly cannot be imposed on them by society. That couples have a right to try whatever means to have children does not mean that children are being treated as objects *owned* by parents. It is not incompatible with moral law to treat such children as gifts as any other child. Conversely it is natural that as we frown upon the breakdown of marriages, we do so as well on any unregulated use of this technology. Whilst liberal countries will not shy away from offering this technology to those who are ready to pay for it, we must not allow legitimate couples to suffer because of slippery slope arguments. Certainly IVF is a service being offered which government has an obligation to regulate or censure; either way the cooperation of the authorities must be ensured to harmonise such decisions and not paralyse people's representatives in parliament. It would mean defining what constitutes a legitimate couple; but that, then, is a different argument. In an ideal world, or in yester world, marriage was the prime stone of societies' edifice; today GPs see the unfortunate scores of young people marrying, separating and settling down on longer relationships. Some are infertile. This behoves the question, 'Do the same patient rights apply to them? Should we offer IVF to them?' Saying no may mean redefining the Hippocratic Oath and Declaration of Helsinki!

New contra-indications and warnings regarding all COX-2 selective inhibitors, including etoricoxib, are available on the MHRA website at http://www.mhra.gov.uk

ARCOXIA®
etoricoxib

ARCOXIA® (etoricoxib)
ABRIDGED PRODUCT INFORMATION
Refer to Summary of Product Characteristics before prescribing
PRESENTATION
Tablets: 60 mg, 90 mg and 120 mg tablets each containing 60 mg, 90 mg or 120 mg of etoricoxib respectively.
USES
Symptomatic relief of osteoarthritis, rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis. Base the decision to prescribe a selective COX-2 inhibitor on an assessment of the individual patient's overall risks.
DOSAGE AND ADMINISTRATION
Take orally with or without food. Onset of action may be faster when administered without food, and should be considered when rapid relief is needed. *Osteoarthritis:*
60 mg once daily. *Rheumatoid arthritis:* 90 mg once daily. *Acute gouty arthritis:* 120 mg once daily for the acute symptomatic period only and limited to a maximum of 8 days. Each dose above is the maximum recommended dose for each condition and should not be exceeded. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, use for the shortest duration possible and use the lowest effective daily dose. Re-evaluate periodically the patient's need for symptomatic relief and response to therapy, especially in osteoarthritis patients. *Hepatic insufficiency: mild (Child-Pugh score 5-6):* do not exceed a dose of 60 mg daily; *moderate (Child-Pugh score 7-9):* **do not exceed 60 mg every other day**. *Renal insufficiency:* No dosage adjustment necessary for patients with creatinine clearance 30 ml/min.
CONTRA-INDICATIONS
History of hypersensitivity to any component of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria or allergic type reactions after aspirin or NSAIDs including COX-2 inhibitors. Pregnancy and lactation. Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score 10). Estimated creatinine clearance <30 ml/min. Children and adolescents under 16 years of age. Inflammatory bowel disease. Congestive heart failure (NYHA II-IV). Patients with hypertension whose blood pressure has not been adequately controlled. Established ischaemic heart disease and/or cerebrovascular disease.
PRECAUTIONS
Gastro-intestinal effects: Upper GI complications (perforations, ulcers or bleedings), some with fatal outcome have occurred in patients taking etoricoxib. Caution is advised in patients most at risk of developing a GI complication with NSAIDs: elderly, those on any other NSAID or aspirin concomitantly, or those with a prior history of GI disease. There is a further increase in the risk of GI adverse effects (GI ulceration or other GI complications) when etoricoxib is taken together with aspirin (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials. *Cardiovascular:* Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, use for the shortest duration possible and use the lowest effective daily dose. Re-evaluate periodically the patient's need for symptomatic relief and response to therapy, especially in those with osteoarthritis. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with etoricoxib after careful consideration. COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued. *Renal effects:* Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. *Fluid retention, oedema and hypertension:* Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Pay special attention to blood pressure monitoring during treatment with etoricoxib. If blood pressure rises significantly, consider alternative treatment. *Hepatic effects:* Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 60 mg and 90 mg for up to one year. Monitor any patient with symptoms/signs of liver dysfunction or in whom an abnormal liver function test has occurred. Discontinue etoricoxib if signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (3 times the upper limit of normal) are detected. *General:* Take appropriate measures and consider discontinuation, if during treatment, patients deteriorate in any of the organ system functions described above. Maintain appropriate medical supervision when treating the elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with etoricoxib. Serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported associated with the use of NSAIDs including other COX-2 inhibitors and cannot be ruled out for etoricoxib. Discontinue at the first signs of hypersensitivity as hypersensitivity reactions (anaphylaxis, angioedema) have been reported. Etoricoxib may mask fever. Use of etoricoxib is not recommended in women attempting to conceive. 'Arcoxia' tablets contain lactose: do not use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. *Interactions (pharmacodynamic): Oral anticoagulants.* Exercise caution when coadministering with warfarin and other oral anticoagulants. Closely monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose changed in patients receiving oral anticoagulants or similar agents, particularly in the first few days. *Diuretics, ACE-inhibitors and Angiotensin II Antagonists:* NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function, the co-administration of an ACE inhibitor or AIIA and cyclo-oxygenase inhibitors may result in further deterioration of renal function including possible acute renal failure, which is usually reversible. Administer cautiously, especially in the elderly. Patients should be adequately hydrated. Consider monitoring renal function at initiation of therapy and periodically thereafter. *Aspirin:* etoricoxib can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administration of low dose aspirin with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of aspirin **above** those for cardiovascular prophylaxis, or with other NSAIDS is not recommended. *Ciclosporin/tacrolimus:* monitor renal function when etoricoxib and either ciclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic): The effect of etoricoxib on the pharmacokinetics of other drugs: Lithium:* the plasma concentration of lithium is increased by NSAIDS, therefore monitor and adjust blood lithium and lithium dosage if necessary. *Methotrexate:* adequate monitoring is recommended for methotrexate-related toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contraceptives (OC):* Administration of etoricoxib 60 mg with an OC containing 35 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC0-24hr of EE by 37%. Administration of etoricoxib 120 mg with the same OC, concomitantly or separated by 12 hours, increased the steady state AUC0-24hr of EE by 50 to 60%. Consider this increase in EE concentration when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives. *Hormone Replacement Therapy:* 120 mg etoricoxib administered with 0.625 mg Premarin™ (Wyeth) for 28 days increased the mean steady state AUC0-24hr of unconjugated estrone (41%), equilin (76%) and 17-á-estradiol (22%). Although the clinical significance is unknown, take into consideration the increase in estrogenic concentration when selecting HRT as the increase in estrogen exposure might increase the risk of adverse events associated with HRT. *Digoxin:* Patients at high risk of digoxin toxicity should be monitored for an increase in digoxin Cmax when etoricoxib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised by sulfotransferases:* Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. It may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil). *Effect of etoricoxib on drugs metabolised by CYP isoenzymes:* Based on *in vitro* studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test. *Effects of other drugs on the pharmacokinetics of etoricoxib.* The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *Ketoconazole:* a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC). *Rifampicin:* Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations, an interaction which may result in recurrence of symptoms. *Antacids:* Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent. *Pregnancy:* contraindicated in the first, second and third trimesters of pregnancy. *Lactation:* contraindicated.
SIDE EFFECTS
The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks, or in post-marketing experience:
[Very common (<1/10) Common (>1/100, <1/10) Uncommon (>1/1000, <1/100) Rare (>1/10,000, <1/1000) Very rare (<1/10,000) including isolated cases)] ***Infections and infestations:*** *Uncommon:* gastro-enteritis, upper respiratory infection, urinary tract infection. ***Immune system disorder:*** *Very rare:* hypersensitivity reactions including angioedema, anaphylactic/anaphylactoid reactions. ***Metabolism and nutrition disorders:*** *Common:* oedema/fluid retention. *Uncommon:* appetite increase or decrease, weight gain. ***Psychiatric disorders:*** *Uncommon:* anxiety, depression, mental acuity decreased. ***Nervous system disorder:*** *Common:* dizziness, headache. *Uncommon:* dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence. ***Eye disorders:*** *Uncommon:* blurred vision. ***Ear and labyrinth disorders:*** *Uncommon:* tinnitus. ***Cardiac disorders:*** *Uncommon:* congestive heart failure, non-specific ECG changes. *Very rare:* myocardial infarction. ***Vascular disorders:*** *Common:* hypertension. *Uncommon:* flushing. *Very rare:* cerebrovascular accident. ***Respiratory, thoracic and mediastinal disorders:*** *Uncommon:* cough, dyspnoea, epistaxis. ***Gastro-intestinal disorders:*** *Common:* gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea. *Uncommon:* abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting. *Very rare:* peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly). ***Skin and subcutaneous tissue disorders:*** *Uncommon:* ecchymosis, facial oedema, pruritus, rash. *Very rare:* urticaria. ***Musculoskeletal, connective tissue and bone disorders:*** *Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness. ***Renal and urinary disorders:*** *Uncommon:* proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of treatment. ***General disorders and administration site conditions:*** *Common:* asthenia/fatigue, flu-like disease. *Uncommon:* chest pain. ***Investigations:*** *Common:* ALT increased, AST increased. *Uncommon:* blood urea nitrogen increased, creatine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased. The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse effects and severe skin reactions.
PACKAGE QUANTITIES AND BASIC NHS COST
60 and 90 mg Tablets: packs of 28 tablets £22.96. 120 mg Tablets: packs of 7 tablets £6.03 and packs of 28 tablets £24.11 **Marketing Authorisation numbers** Tablet 60 mg PL 0025/0422. Tablet 90 mg PL 0025/0423. Tablet 120 mg PL 0025/0424 **Marketing Authorisation holder** Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK **PDate of review:** June 2005 ® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA. Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

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Imaging Ham

continued from page 2

Thus, the benefits of adequate rest and an aggressive strengthening rehabilitation program cannot be overstated. Also at the microscopic level, the HMC is composed of a large proportion of type 2 "Fast-Switch" muscle fibres, which are capable to producing rapid tensile strength but are more susceptible to myofibrillar strain injury.

Even minor injury in the HMC results in ultrastructural change in which torn myofibrillar Z bands cause protein degradation with release of protein-bound ions leading to oedema; if this of sufficient magnitude, it can be visualized at imaging.

With minor injuries, microscopic analysis shows haemorrhage at these sites of disruption in the acute phase (<24 hours after disruption), followed by an inflammatory reaction whose time of occurrence is variable (usually at day 2) with laying down of fibrous tissue by day 7 to commence the formation of scar tissue. Such tissue first becomes visible as early as 14 days following initial insult, principally manifesting with low signal intensity on MRI and hypoechogenicity on US. At this point, the muscle has regained over 90% of its function. Nevertheless, given that fibrosis results in retraction, the optimal muscle length is altered, and, consequently, so is the ability of the muscle to maximally contract, which makes the HMC more susceptible to future injuries.

The most serious acute injury of the HMC is avulsion, which in adults usually involves the tendon but not the bone. This pattern of injury occurs more commonly at the ischial tuberosity than at the distal insertions. In such a case, avulsion almost always involves the conjoint tendon (biceps femoris and semitendinosus muscles) and often results in either complete or incomplete tearing of the semimembranosus (Figure 3). US may have difficulty visualising these injuries due to the depth the conjoint tendon beneath large gluteal muscles (especially in athletes). However, in most cases and with some examiner experience, even incomplete tears and common tendon degeneration can be readily visualised with ultrasound (Figure 4). Imaging allows accurate assessment of the degree of tendon retraction and of the tendon or bony edge for the surgeon contemplating primary surgical repair.

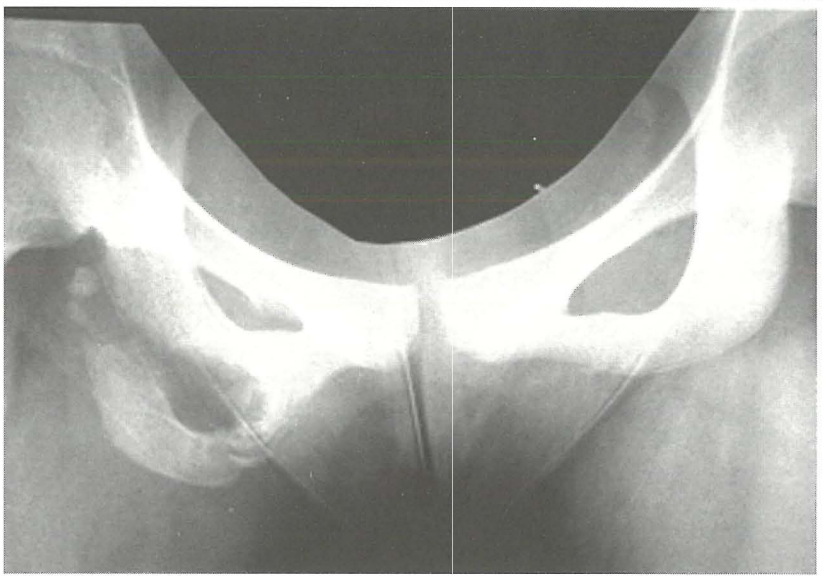

Figure 5. *Old avulsion injury involving the right ischium that must have occurred prior to epiphyseal fusion.*

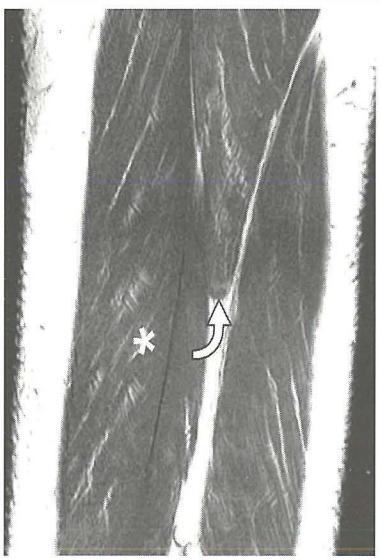

Figure 6. *The patient presented with acute distal posterior knee pain during rehabilitation following ACL reconstruction. Coronal MR image shows avulsion of the semitendinosus tendon (arrow), with retraction of the muscle. The long head of the biceps femoris is located laterally (*), and the semimembranosus medially.*

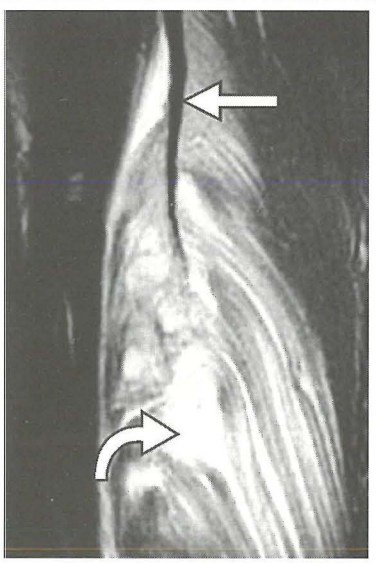

Figure 7. *26-year-old professional football player who presented with recurring hamstring strains and prolonged rehabilitation periods. Coronal MR image shows hyperintensity (curved arrow) in the MTJ of the biceps femoris in keeping with myofibrillar disruption and retraction from the central tendon slip (straight arrow).*

nstring Injury

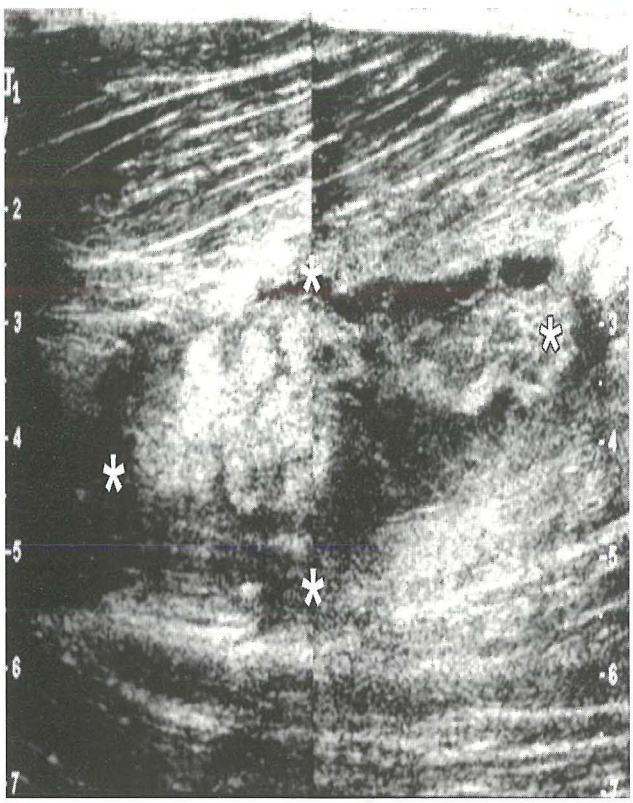

Figure 8. *Sagittal US image demonstrates an abnormality with mixed echogenicity that corresponds to the MTJ disruption in the biceps femoris. * = boundaries of the area of disruption.*

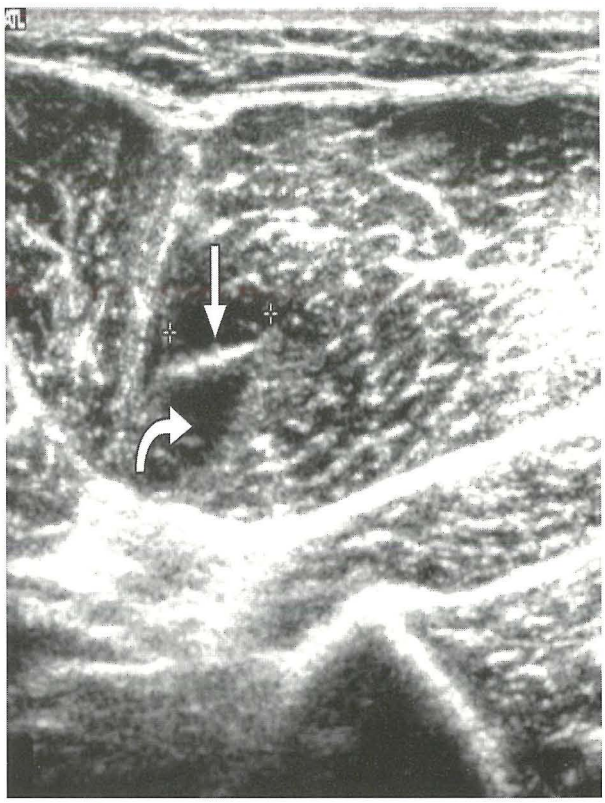

Figure 9. *Transverse US image demonstrates oedema (curved arrow) around the MTJ (straight arrow) in the semitendinosus muscle.*

In children, proximal avulsion more commonly involves bone with detachment of part of or the whole ischium, which has not yet fused with the other pelvic bones at the growth plate (Figure 5).

Distal avulsions are uncommon injuries but are most often seen in water skiers and football players. Avulsions of each tendon insertion have been reported, although avulsion of the semitendinosus is probably the most common (Figure 6). Avulsion usually occurs in the setting of prior or chronic injury, with abnormal tendon morphologic features or degeneration being the most likely predisposing factors. MR imaging accurately displays distal tendonous avulsion and the degree of retraction. However, US has superior spatial resolution, which, in combination with the superficial nature of the tendon, makes application of this modality ideal. Dynamic assessment, which is only possible with ultrasound can provide additional information about tendon integrity.

Partial tearing of the HMC is often referred to as a strain. Most strains occur in the region of the musculo-tendonous junction (MTJ) (Figure 2), which is the weakest link in the muscle complex. The MTJ is not a distinct area but a 10–12cm zone of transition in which muscle fibrils attach to the tendon. These tears can occur in any of the HMC muscles but are most common in the biceps femoris. On MR Imaging, the high signal intensity of oedema, fluid, and blood products characteristically dissects along disrupted fibrils creating a feathered appearance (Figure 7). The low echogenicity of muscle oedema is seen at US (Figures 8 & 9).

MR imaging and US are the imaging modalities of choice for assessing HMC injury. Experience, in combination with knowledge of the HMC anatomy, will assist the musculoskeletal radiologist in making an accurate and useful contribution to the treatment of athletes at all levels of participation.

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References: 1. Marie PJ< Ammann P, Boivin G, et al. Calcif Tissue Int. 2001;69:121-129. 2.European Summary of Product Characteristics.
3. Meunier PJ, Roux C, Seeman E, et al. N Engl J Med. 2004;350:459-468. 4. Rizzoli R, Reginster JY Diaz-Curiel M, et al. Osteoporos Int. 2004;15:S18. Abstract OC39.

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