NEWSPAPER POST

TheSynapse

The Medical Professionals' Network

MEDICAL IMAGING

Imaging Pyelonephritis - Part I

by **Pierre Vassallo**
MD PhD FACA Artz für Radiologie
Consultant Radiologist

Urinary tract infections constitute a common cause for medical consultation and may occasionally require emergency admission to hospital. In adults, diagnosis of urinary tract infection is typically based on characteristic clinical features and abnormal laboratory values. Imaging is usually reserved for patients who do not respond to therapy, for those with recurrent infections and for those whose clinical presentation is either atypical or potentially life threatening.

Urinary tract infection typically originates in the urinary bladder (lower urinary tract); when it migrates to the kidney via the ureter or is seeded there haematogenously, a tubulointerstitial inflammatory reaction ensues, involving the renal pelvis and parenchyma. The condition is characterized as pyelonephritis.

Classic symptoms of pyelonephritis include an abrupt onset of chills, fever (temperature of 100°F or greater), and unilateral or bilateral flank pain with posterior costovertebral ("renal angle") tenderness. These "upper tract signs" are often accompanied by dysuria and urinary frequency and urgency. Furthermore, acute pyelonephritis may cause gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, and diarrhoea, which confound the diagnosis. Laboratory findings include pyuria, granular or leukocytic casts, bacteriuria, and a positive urine culture. Blood tests may show leukocytosis with a neutrophilic shift, elevated erythrocyte sedimentation rate, elevated C-reactive protein levels, and occasionally positive blood cultures that grow the same organism as cultured from the urine.

Immediately after the collection of urine for culture and antibiotic sensitivity testing, antibiotic therapy is started. Most patients respond successfully to antibiotics and do not require imaging studies or further intervention. In select clinical scenarios, however, diagnostic imaging plays a role, including *(a)* to assist in the diagnosis of acute pyelonephritis when the patient fails to respond to appropriate therapy within the first 72 hours (occurs in approximately 5% of patients), *(b)* to look for previously occult structural or functional abnormalities that may require intervention, *(c)* to assess those patients at significant risk for more severe life-threatening complications (e.g. diabetic, elderly, or immunocompromised patients), *(d)* to characterize the severity of the infection to direct future therapy or interventions, and *(e)* to evaluate the extent of organ damage subsequent to a resolved acute infection. Pyelonephritis is but one form of interstitial nephritis. The most common organism causing UTIs is Escherichia coli.

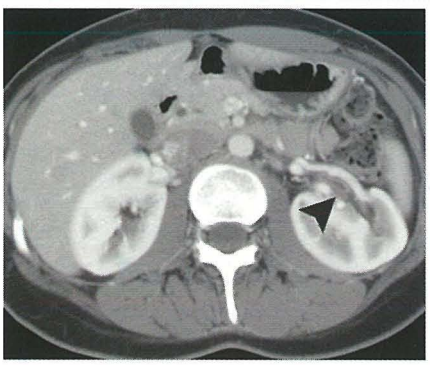


Figure 1. *CT scan showing unilateral pyelitis in a patient with suspected acute bacterial pyelonephritis*

The pathophysiology of acute, ascending pyelonephritis is best discussed as a continuum of disease. The bladder is originally inoculated with an infectious organism, which then migrates up the ureter to the central collecting system.

continues on page 2

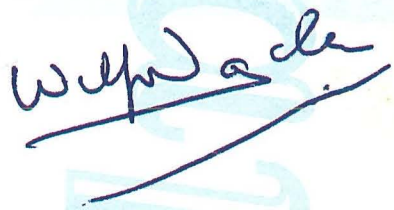
Editor's Word

Dear Friends and Colleagues,

Welcome to issue 2 of TheSYNAPSE magazine for this year. As professionals in the fields of medicine, we are living in interesting times with rapid developments in all aspects of our professional life as well as changes in the society we live in. The future is filled with challenges and opportunities.

In this edition we tackle a number of issues with a range of very interesting and informative articles spanning from the era of the Egyptians to molecular genetics which promises to play an ever growing important role in our practice. We also have a number of review articles which keep us up to date as well as other announcements of interest to you.

I wish to thank all contributors, advertisers, editorial and administrative staff as well as all readers whose work and support help make TheSYNAPSE a success.



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Editor: Wilfred Galea
Scientific Editor: Ian. C. Ellul
Administration Manager: Carmen Cachia
Designer: Conrad Bondin

Imaging Pyelonephritis - Part I

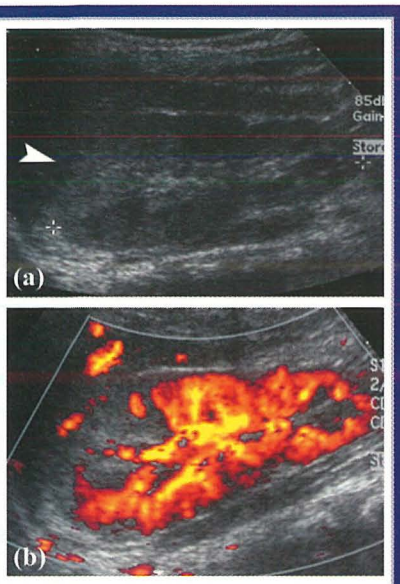

Figure 2. (a) *US scan shows a wedge-shaped hyperechoic focus (arrowhead) in the upper pole of the right kidney related to acute bacterial pyelonephritis.* **(b)** *Colour flow US image demonstrates diminished flow through the involved area.*

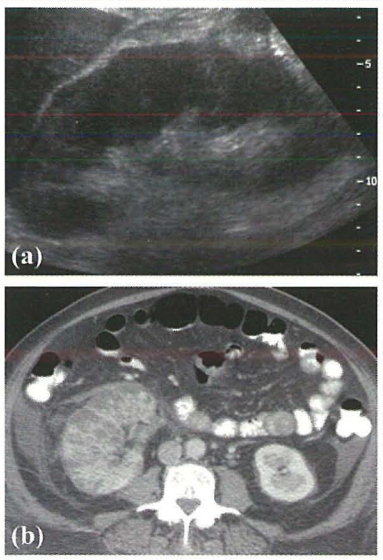

Figure 3. (a) *US image demonstrates a slightly enlarged right kidney that is otherwise unremarkable, belying the advanced disease.* **(b)** *CT scan shows the enlarged kidney with multiple small low-attenuation foci from abscess pockets, findings that prompted nephrectomy.*

This ascent occurs even in the absence of reflux, owing to special virulence properties of the bacteria, such as the adhesin P fimbriae and endotoxins. The endotoxins are believed to inhibit ureteral peristalsis by blocking the – adrenergic nerves within smooth muscle, thus creating a functional obstruction. The obstruction compromises the forward flow of urine, which is a normal protective mechanism against upper urinary tract infection. An infected, inflamed ureter and renal pelvis are accurately characterized as ureteropyelitis and occasionally can be demonstrated radiologically before renal parenchymal changes evolve (Figure 1). Continuing their retrograde ascent, bacteria enter the renal tubules at the papillary tip and cause an inflammatory response that extends up the tubule and into the renal interstitium.

Abdominal radiographs were routinely obtained as the first component of an intravenous urogram, IVU; however, use of CT has overtaken that of radiography in nearly all institutions. The scout radiographs have been used in the past to detect urinary tract gas and calcifications, but pitfalls included unreliable differentiation of abdominal bowel gas from urinary tract gas and nonvisualization of small urinary tract calcifications overlying normal bony structures such as transverse processes. The IVU delineates the anatomy of the pelvi-caliceal system and provides an overview of the urothelial system from the kidneys to the urinary bladder. Findings seen in cases of acute kidney infections include renal enlargement, striated or delayed nephrograms (i.e. renal parenchymal enhancement), delayed caliceal appearance time, and dilatation or effacement of the collecting system. The weaknesses of excretory urography include the inability to characterize renal masses (i.e. as cysts, neoplasms, or abscesses), the lack of fine parenchymal detail, and the dependency on functioning kidneys. In addition, several studies have demonstrated that only about 25% of patients with acute pyelonephritis have abnormal findings on an IVU. Therefore, more advanced imaging techniques are generally preferred. In addition, urinary tract stones that may accompany or cause pyelonephritis, are frequently only be visible on CT without IV contrast.

Ultrasonography (US) is frequently used as a first-line diagnostic tool to evaluate the urinary tract in patients with symptoms of pyelonephritis. Most patients with clinically suspected pyelonephritis have negative results from US, with several studies showing US abnormalities in only 24% of patients with pyelonephritis.

continues on page 26

NEW IN SMOKING CESSATION

THE POWER TO HELP THEM QUIT. FINALLY.[1-4]

- A **new class** of oral prescription therapy with a unique dual action:[1,2,5]
  - **Partial agonist** action: Reduces craving and withdrawal symptoms[§]
  - **Antagonist** action: Reduces the satisfaction associated with smoking[§]
- Significantly **higher quit rate** vs. buproprion or placebo at 12 weeks:[1-3]
- Favourable safety and tolerability profile in approximately 4,000 treated smokers[6]

[§]Based on Minnesota Nicotine Withdrawal Scale (MNWS), Brief Questionnaire of Smoking Urges and modified Cigarette Evaluation Questionnaire.

NAME OF THE MEDICINAL PRODUCT: CHAMPIX 0.5 mg and 1 film-coated tablets. **QUALITATIVE AND QUANTITATIVE COMPOSITION:** Each film-coated tablet contains 0.5 mg or 1 mg of varenicline (as tartrate). **PHARMACEUTICAL FORM:** Film-coated tablet. 0.5 mg and 1 mg film-coated tablets: White, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 0.5" or "CHX 1.0" on the other side. **CLINICAL PARTICULARS: Therapeutic indications:** CHAMPIX is indicated for smoking cessation in adults. **Posology and method of administration:** Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support. CHAMPIX is for oral use. The recommended dose is 1mg varenicline twice daily following a 1-week titration as follows: Days 1-3: 0.5mg once daily. Days 4-7: 0.5mg twice daily. Day 8 - End of treatment: 1mg twice daily. The Patient should set a date to stop smoking. CHAMPIX dosing should start 1-2 weeks before this date. Patients who cannot tolerate adverse effects of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily. CHAMPIX tablets should be swallowed whole with water. CHAMPIX can be taken with or without food. Patients should be treated with CHAMPIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily may be considered. No data are available on the efficacy of an additional 12 weeks course of treatment for patients who do not succeed in stopping smoking during initial therapy or who relapse after treatment. In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered. *Patients with renal insufficiency:*No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment. For patients with moderate renal impairment who experience adverse events that are not tolerable, dosing may be reduced to 1 mg once daily. For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population. *Patients with hepatic impairment:* No dosage adjustment is necessary for patients with hepatic impairment. *Dosing in elderly patients:* No dosage adjustment is necessary for elderly patients. Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient. *Paediatric patients:* CHAMPIX is not recommended for use in children or adolescents below 18 years of age due to insufficient data on safety and efficacy. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** *Effect of smoking cessation:* Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates. Smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. There is no clinical experience with CHAMPIX in patients with epilepsy. At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.**Undesirable effects:** Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse events associated with study drug treatment or those possibly associated with nicotine withdrawal. Clinical trials included approximately 4,000 patients treated with CHAMPIX for up to 1 year (average exposure 84 days). In general, when adverse reactions occurred, onset was in the first week of therapy; severity was generally mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions. In patients treated with the recommended dose of 1mg BID following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation. The treatment discontinuation rate due to adverse events was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo). Below, all adverse reactions, which occurred at an incidence greater than placebo are listed by frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)).Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Very common: Abnormal dreams, insomnia, headache, nausea. Common: Increased appetite, somnolence, dizziness, dysgeusia, vomiting, constipation, diarrhoea, abdominal distension, stomach discomfort, dyspepsia, flatulence, dry mouth, fatigue. Uncommon: Bronchitis, nasopharyngitis, sinusitis, fungal infection, viral infection, anorexia, decreased appetite, polydipsia, panic reaction, bradyphrenia, thinking abnormal, mood swings, tremor, coordination abnormal, dysarthria, hypertonia, restlessness, dysphoria, hypoaesthesia, hypogeusia, lethargy, libido increased, libido decreased, atrial fibrillation, palpitations, scotoma, scleral discolouration, eye pain, mydriasis, photophobia, myopia, lacrimation increased, tinnitus, dyspnoea, cough, hoarseness, pharyngolaryngeal pain, throat irritation, respiratory tract congestion, sinus congestion, post nasal drip, rhinorrhoea, snoring, haematemesis, haematochezia, gastritis, gastrooesophageal reflux disease, abdominal pain, change of bowel habit, abnormal faeces, eructation, aphthous stomatitis, gingival pain, tongue coated, rash generalised, erythema, pruritus, acne, hyperhidrosis, night sweats, joint stiffness, muscle spasms, chest wall pain, costochondritis, glycosuria, nocturia, polyuria, menorrhagia, vaginal discharge, sexual dysfunction, chest discomfort, chest pain, pyrexia, feeling cold, asthenia, circadian rhythm sleep disorder, malaise, cyst, blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased, liver function test abnormal, platelet count decreased, weight increased, semen abnormal, C-reactive protein increased, blood calcium decreased. Post-marketing cases of myocardial infarction have been reported in patients taking varenicline. **Shelf life:** 2 years. **Supply classification:** POM. **MARKETING AUTHORISATION HOLDER:** Pfizer Limited, Ramsgate Road, Sandwich Kent, CT13 9NJ, UK. **LOCAL REPRESENTATIVE OF THE MARKETING AUTHORISATION HOLDER:** V.J. Salomone Pharma Ltd., 79, Simpson Street, Marsa HMR 14, Tel : +356 21220174. **MARKETING AUTHORISATION NUMBERS:** EU/1/06/360/001 – 011 **DATE OF REVISION OF THE TEXT:** April 26th, 2007

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Pfizer

New oral prescription medicine

CHAMPIX®

varenicline tartrate

QUITTING POWER

CHM-MT-2008-06

Molecular Genetic Testing

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

Breast cancer is one of the most common cancers in the world. The incidence in Malta is around 94 per 100,000 population.[1] Breast cancer is a complex and heterogeneous disease caused by the interaction of various genetic and environmental factors. The identification of breast cancer causative genes has been an ongoing process both because of the magnitude of the problem and as an opportunity to reduce the public health impact of the disease, as well as the utilisation of breast cancer as a model to study the molecular basis of cancer.

Though breast cancer that clusters in families is not infrequent, hereditary causes are only responsible for 15-20% of these cases.[2] Other factors that can be correlated with familial clusters include localised environmental factors (carcinogens), culturally motivated behaviour that can alter risk factors such as age of first born and socioeconomic influences that could for example influence dietary habits.

Contrary to non-hereditary breast cancer that clusters in family, inheritable breast cancer has several distinctive clinical features, such as a lower age of onset, higher prevalence of bilateral disease and the presence of associated tumours in affected individuals such as ovarian, prostate, endometrial, colon and sarcomas.[3,4]

Genes that have been implicated with an increased risk of breast cancer include:

- The BRCA1 or BRCA2 mutation syndromes
- Ataxia telangiectasia (AT) gene
- Li-Fraumeni syndrome due to TP53 mutation
- Mutations in CHEK2
- Cowden syndrome due to PTEN mutations
- Peutz-Jeghers syndrome.

Mutations in each of these genes produce different clinical phenotypes of characteristic malignancies and in some instances, associated nonmalignant abnormalities. All of these mutations, except the ATM gene, are inherited in an autosomal dominant manner.

BRCA1 and BRCA2 genes

The BRCA1 gene is located on the long arm of chromosome 17 whilst BRCA2 is located in the long arm of chromosome 13. Both these genes are tumour suppressor genes. Tumour suppressor genes control the cell cycle by either regulating the cell cycle or else promote apoptosis (programmed cell death). Loss of both functional copies of a tumour suppressor gene causes a malignant change in the involved cells.

The BRCA1 gene is around 100Kbp long and composed of 24 exons. On the other hand the BRCA2 gene is around 70Kbp in length and composed of 26 exons. The relatively large size and the large number of known pathological mutations in both genes (over 800 in each gene), creates a problem in the identification of mutations in populations where no knowledge of the prevalent mutations exist, such as Malta.

Ataxia-telangiectasia

Ataxia-telangiectasia is a rare inherited disorder of childhood affecting the nervous system, immune system and other body systems. It is characterised by progressive ataxia from early childhood together with telangiectasia occurring in the eyes and on the surface of the skin. Due to weakening of the immune systems, chronic lung infections, leukemias and lymphomas are common.

Ataxia-telangiectasia is due to mutations in the ATM gene, situated on the long arm of chromosome 11 and is around 150Kbp in length. The disorder is inherited in an autosomal recessive pattern, with carriers of the condition having an increased risk of breast cancer. Ataxia-telangiectasia occurs in 1 in 40,000 to 100,000 people worldwide with a carrier rate of 0.6 to 1%.

Li-Fraumeni syndrome

The Li-Fraumeni syndrome (LFS) is a syndrome associated with soft-tissue sarcoma, breast cancer, leukaemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex and brain. The syndrome is caused by mutations in the transcription factor p53 coded by the tumour protein 53 gene, located on the short arm of chromosome 17 and around 20Kbp in length. p53 reacts to various cellular stresses in order to regulate target genes that induce cell cycle arrest, apoptosis, DNA repair and changes in metabolism. Loss of p53 function increases the risk of multiple primary cancers. Though p53 loss in somatic tumours is very common, the hereditary form i.e. LFS, is very rare, with around 400 families registered worldwide and around 392 different germline mutations identified.

Antiviral Drug resistance of

by **Tanya Melillo Fenech** *MD MSc (HSM) Dip (HSM)*
Principle Medical Officer, Infectious Disease Prevention and Control Unit
Department of Health Promotion and Disease Prevention

H1N1 are predominant in epidemics worldwide and the discovery of antiviral drug resistance was a new phenomenon this winter.

Compared to the previous last 3 winter seasons, this year the presence of oseltamivir (Tamiflu®) resistance viruses circulating in the community was detected in a number of European Countries (Norway, Denmark, UK, France, Finland, Netherlands, Portugal, Sweden and Germany). It has also been detected in USA, Canada and now China. However Japan who widely prescribes oseltamivir, have not seen an increase in resistance.

Preliminary results of the surveillance of antiviral drug susceptibility of seasonal influenza viruses circulating in Europe have shown a significant proportion (13%) of the Type A (H1N1) viruses - which are the predominant virus this season - to be resistant to oseltamivir but retain sensitivity to zanamivir (Relenza®) and amantadine/rimantadine. In North America the frequency of isolation so far has been 6% in Canada and 8% in USA and Hong Kong.

The resistant viruses carry the same mutation, the substitution of histidine by tyrosine at residue 274 (H274Y) of the neuraminidase protein, which confers high level resistance to oseltamivir.

The resistant viruses have been isolated from both adults and children, ranging from 1 month to 53 years in age, with the majority of viruses being isolated from adults within European countries. So far, there is no information that any of these viruses, in any country, has been obtained from a person who has either been previously treated with oseltamivir, or been in close contact with another individual who has been treated with oseltamivir.

in Hereditary Breast Cancer

CHEK2 Mutations

The CHK2 checkpoint homolog (CHEK2) gene is located on the long arm of chromosome 22 and is about 22Kbp in length. Checkpoint kinase 2 is a tumour suppressor gene that regulates cell growth. It is activated when the DNA becomes damaged by agents such as toxic chemicals, radiation or ultraviolet rays. In response to DNA damage, the CHK2 protein interacts with several other proteins, including tumor protein 53, to halt cell growth and determine whether the DNA damage can be repaired, otherwise apoptosis sets in. Germ line mutations in the CHEK2 gene have been associated with some cases of breast cancer, in particular, a single mutation (1100delC) is associated with a moderately increased risk of breast cancer in European populations.

Cowden Syndrome

Cowden syndrome is a relatively rare disorder, mainly characterised by noncancerous, tumour-like growths called hamartomas (typically occurring during the late 20's), but with an increase risk of certain cancers such as breast, thyroid and endometrial carcinoma. In addition, there is a higher than normal risk of macrocephaly, mental retardation and non-cancerous brain tumours.

The majority of the Cowden Syndrome cases are associated with mutations in the Phosphatase and TENsin homolog (PTEN gene), situated in the long arm of chromosome 10 and about 100Kbp in length. Similarly to the BRCA and TP53, PTEN is also a tumour suppressor gene and thus has similar functions in that it stops cell growth and induces apoptosis. It is estimated that the worldwide incidence of Cowden Syndrome is of 1 in 200,000.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is a rare disorder characterised by hamartomatous polyposis of the entire digestive tract, an increased risk for tumors of the ovary, cervix and pancreas, and a higher risk for cancer of the breast and of the thyroid. It is a rare condition with a prevalence of under 1 in 50,000 and is inherited in an autosomal dominant pattern. In 70% of families, the syndrome is due to mutations in the STK11 gene on chromosome 19.

Diagnostic Criteria for Hereditary Breast Cancer

In addition to the breast cancer cases that show a clear pattern of inheritance, another 25% of breast cancer cases have some family history. It is thus clear that genetic testing for all breast cancer cases would produce a large number of negative tests. It is therefore imperative that one sets defined criteria so as to select the cases that warrant genetic testing as well as to formulate proper risk assessment.

Hereditary breast cancer is highly suspected when:

1. Present in more than two generations
2. Early age of onset (<40years)
3. Present in a male relative or if a male relative has early onset prostatic carcinoma
4. Patient or relatives suffered from other types of cancer, congenital malformations or genetic syndromes.

Is there a need for Predictive Genetic Testing in Hereditary Breast Cancer Cases?

Predictive genetic testing for hereditary breast cancer has a number of positive effects that include:

- Clarification of the actual risk evaluation
- Target prevention efforts to the identified carriers (intensified screening procedures, prophylactic hormonal therapy and prophylactic mastectomy with reconstruction)
- Exclude the non-carriers and thus reduce the psychological stress
- Knowledge that there is no risk for the children of proven non-carriers.

Though the advances in molecular biology techniques have increased the ability to be able to identify mutations within specific genes and thus identify individuals at risk, the results obtained can sometimes be ambiguous. This may happen because of two circumstances i.e. when no mutation is identified in a family where no known mutation is present and in those cases where a new polymorphism is identified but its pathological status is not clear. These cases present a dilemma for the counselor and the surgeon since although a family history is obviously present, no definite molecular defect is identified.

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Influenza Viruses in Europe

The frequency of oseltamivir resistance in H1N1 viruses in the current influenza season has been unexpected, and the reason why a higher percentage of these viruses are resistant is currently unknown.

This development has caused experts to do a risk assessment of the situation and the important conclusion made recently by WHO and European Centre for Disease Control and Prevention was that:

- The new H1N1-H274Y viruses have limited pandemic potential as they are a variant of a widely circulating strain. This differs from a pandemic scenario, which is likely to be caused by a completely novel strain of influenza virus.
- Though guarantees of effectiveness against an unknown virus cannot be made there is no reason to believe that oseltamivir will be ineffective against novel strains.
- Equally it is important to appreciate that H1N1-H274Y is a human seasonal virus and must not be confused with avian influenza viruses notably the similarly named A/H5N1 which causes avian influenza in poultry.

Seasonal Influenza

There is currently medium influenza activity in 18 countries in Europe. In most countries influenza activity is unchanging or declining. Compared to influenza A, the proportion of influenza B has increased from 14% in the beginning of this year to 37% by the last week in February. The large majority of the total virus detections since last September were influenza A (87%) of which about 99% were of the H1 subtype.

America has noticed a mismatch between the components in this season's vaccine and the circulating influenza B and A (H3N2) subtype.

WHO has just issued the new composition for the upcoming vaccine for 2008/2009 and it will be made up of 3 new strains:

- **H1N1**: A/Brisbane/59/2007
- **H3N2:** A/Brisbane/10/2007
- **B:** B/Florida/4/2006


A breakthrough in hypertension management:
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- Powerful BP reductions alone and in combination[2,5,6]
- Double-digit BP reductions beyond 24 hours[5]
- Placebo-like tolerability[2,5,6]

Presentation: Rasilez film-coated tablets containing 150mg and 300mg of aliskiren. **Indications:** Treatment of essential hypertension. **Dosage:** 150mg to 300mg once daily with a light meal, alone or in combination with other anti-hypertensive agents. No adjustment of initial dose require in elderly (>65 years), renal and liver impairment. Not recommended in patients under 18 years of age. **Contraindications:** • Hypersensitivity to the active substance or excipients. • Pregnancy. **Warnings/Precautions:** • Increased risk of hyperkalaemia in patients receiving other RAS agents, and/or those with reduced kidney function and/or diabetes mellitus • Caution in patients with heart failure • Close medical supervision in patients with marked volume- and/or salt-depleted patients due to risk of hypotension • Caution in patients with severe renal dysfunction, renal artery stenosis, a history of dialysis, nephrotic syndrome, or renovascular hypertension • Not recommended during pregnancy or when planning to become pregnant, to be discontinued if pregnancy occurs. • Not recommended in breastfeeding women. • In event of severe and persistent diarrhea, Rasilez should be stopped. **Interactions:** • Monitoring when used concomitantly with furosemide • Interaction with ketoconazole • Concomitant treatment with drugs that may increase serum potassium levels • Possible interaction with digoxin, irbesartan, St. John's wort, and rifampicin • Meals with high fat content substantially reduce absorption. **Adverse reactions:** • Common: diarrhea • Uncommon: Rash • Rare: Angioedema. • Laboratory values: decrease in haemoglobin and haematocrit, increase in serum potassium. Please refer to SmPC for a full list of adverse events. **Legal Category:** POM **Pack sizes:** 28 film-coated tablets **Marketing Authorisation Holder:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **Marketing Authorisation Numbers:** EU/1/07/405/001 - 020. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma, P.O. Box 124, Valletta, VLT1000, Malta. Tel +356 22983217.

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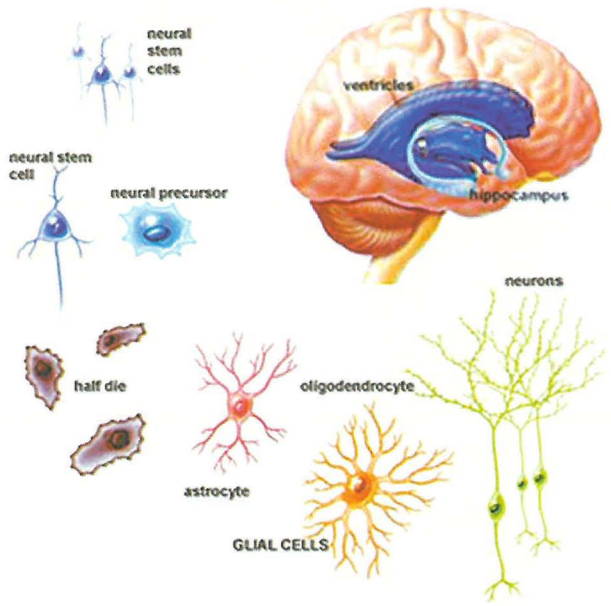
Neural Stem Cells and the Aging Brain – Part II

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

Neural Stem Cell Therapy

Neural stem cells have a number of potential applications in treating neurodegenerative disorders. Neurons lost during the disease process may be replaced either by facilitating the proliferation of neural stem cells already present in the brain (endogenous replacement) or else by transplantation of neural stem cells in the damaged area of the brain (exogenous replacement). For transplantation to be viable, cells have to fulfil three important criteria. Firstly, the transplanted cells must survive the procedure. Secondly, the transplanted neural stem cell has to develop in the required type of brain cell and finally, the transplanted cell must make the necessary connections to survive and be part of the existent neural network. If transplantation occurs in a diseased brain, the newly transplanted cell must also survive in the diseased environment. Although recent studies using animal models showed promising results, exogenous transplantation of neural stem cells is still a long way to go. One of the major limitations is that it is still difficult to produce the type of replacement cell needed following differentiation *in vivo*.



Transplant studies in humans have mostly used embryonic stem cells rather that neural stem cells. These have pluripotent characteristics giving them the ability to form all types of cells in the mature adult. However the use of stem cells having embryonic origin is highly controversial as it presents difficult moral and ethical issues. Moreover, success using this approach was limited especially in neurodegenerative disorders characterised by diffuse neuronal damage such as in Alzheimer's disease. The high oxidative stress coupled by the presence of the neurotoxic beta-amyloid protein also inhibits the survivability of transplanted stem cells.

A less invasive route would be the mobilisation of endogenous stem cells to replace the damaged ones. Indeed, there is substantial evidence indicating that neural stem cells are capable of responding to environmental cues that promote neurogenesis. Various studies show that neural stem cells are highly responsive to growth factors that affect the proliferation and survival of these cells. Such factors include the fibroblast growth factor and the epidermal growth factor, both of which have shown to act as activators of neural cell proliferation.[1] While treatment with growth factors can be regarded as a potential therapeutic approach, it is limited by the fact that neural stem cells will proliferate only to a certain number of cell divisions. Furthermore, neural stem cells in the aging brain exhibit decreased ability to proliferate under normal conditions and thus the ability of growth factors to stimulate cell proliferation may also be reduced in the aging brain.

Many factors regulate adult neurogenesis, and the issue of possible environmental influence on neural cell proliferation in the adult brain has been particularly investigated in the hippocampus because of its role in learning and memory processes and its involvement in Alzheimer's disease. Various research reports show that hippocampal-dependent learning, such as spatial memory formation, promotes neurogenesis in the hippocampus where the generation of new neurons is important in memory formation.[2] Animal models placed in an enriched environment including enhanced social interactions, show an increase in the number of hippocampal neurons. Similarly, increased exercise also showed increased hippocampal-associated neurogenesis possibly due to an increase in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) mRNA in the hippocampus.[3,4] Interestingly, hippocampal neurogenesis is significantly inhibited in major depression, and anti-depressant therapies including drugs such as tricyclic antidepressants and selective serotonin/noradrenaline reuptake inhibitors and electroconvulsive therapy reverse it.[5] Whether this reduction in neural cell proliferation is directly correlated to changes in the mood pattern is still subject to further research.

The effects of social drugs such as alcohol and nicotine on adult neurogenesis have also been subject to extensive research. The effects of alcohol on the brain during development are well known especially during pregnancy – extensive use of alcohol results in foetal alcohol syndrome in which the brains of infants are significantly smaller in size then their normal counterparts. In fact, embryonic stem cells are highly sensitive to alcohol exposure, demonstrating increased apoptosis.

continues on page 10

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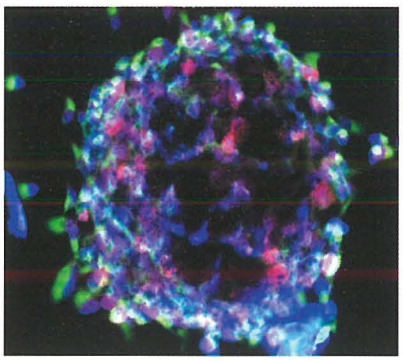
Neural Stem Cells and the Aging Brain – Part II

continued from page 8

The effect of alcohol on adult brain neurogenesis is typically studied in the hippocampus, as hippocampal neurogenesis is believed to be essential in memory formation and chronic alcohol exposure leads to memory impairment. Rodent models of binge drinking have shown that chronic ethanol exposure prevents cell proliferation and survival of hippocampal neural stem cells.[6] Nicotine was also reported to impair neural cell proliferation in a dose-dependent manner. When rats were infused with nicotine for two weeks in a concentration normally found in adult heavy smokers, it was found that together with a significant reduction in cell proliferation in the hippocampus, spatial memory was also impaired.[7] Although more research is necessary to determine the cellular processes involved, these studies continue to highlight the harmful effects of alcohol and nicotine on the brain especially when neural cell proliferation is already compromised by old age or disease.

Changing the Cell Cycle

One approach that may be used to stimulate neural cell proliferation is to stimulate proteins that directly participate in cell division (cell cycle proteins). Potential targets are proteins known as telomeres and the enzyme that catalyses telomere lengthening, telomerase. Telomeres have long been recognised as being important in maintaining gene integrity by capping the ends of chromosomes and thus preventing DNA degradation.[8] However, telomere length also acts as a sort of a biological clock, regulating the number of cell divisions before the cell becomes inactive. Telomere length is maintained by the enzyme telomerase, which adds a short DNA sequence to the end of telomeres. The activity of this enzyme is maintained during adulthood in proliferating cells but is inactive in mature cells (cells that have differentiated completely). As aging progresses, telomere proteins become shorter thereby limiting the number of cell divisions to a finite number before permanent growth arrest. Therefore, changes in



telomere length and telomerase activity can drastically alter the lifespan of cells.

The rate of telomere shortening is sensitive to many factors and stressors that accompany old age. Of particular importance is oxidative stress which has been implicated in promoting the acceleration of telomere loss and reduced life span in a number of biological systems. Interestingly, shortened telomere length is now being linked to several age-related diseases which are believed to have oxidative stress as a causative factor, such as vascular dementia and atherosclerosis.[9] Oxidative stress has also been linked to Alzheimer's disease. Beta-amyloid protein, which is found in high quantities in the brains of these patients, is believed to act as a neurotoxic agent by causing oxidative stress in neurons leading to loss of neural cell proliferation in the hippocampus.[10]

Conclusion

Several strategies are currently being studied and developed in the hope of repairing damage associated with age-related neurodegenerative disorders. Among these, neural stem cells seem to offer a potential therapeutic strategy for some of the most devastating disorders which afflict the aging brain. As with any disease, the development of new therapeutic approaches relies heavily on extensive knowledge of the biological systems involved, and the ramification of alterations within the system following the onset of disease. Continued research is therefore necessary to fully understand the pathways critical for neural stem cell survival and differentiation and their significant role in the aging and diseased brain. This clearly represents one of the most important future challenges for basic and clinical neuroscientific research.

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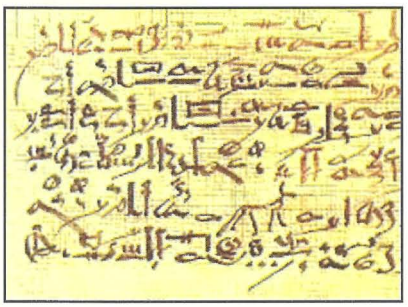
Ancient Egyptian Medicine

Part IV [1] – Medical Papyri

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

Much of the detailed information about the extent of the practice of medicine of the Ancient Egyptians comes from the rich source of textual material that has been found over the years. The main textual material comes from several Ancient Egyptian papyri which have a medical content. Most of these documents relate to diseases, remedies and the structure of the body as well as incantations and magic spells used as treatments in many cases. Most of these were discovered in the 19th and early 20th centuries, and no doubt these are only the tip of the iceberg. Many tracts must have been destroyed down through the years by natural phenomenon as well as by human intervention such as tomb robbers, military invasions and such like.



The Edwin Smith Papyrus is, without a doubt, one of the most important documents pertaining to medicine in the ancient Nile Valley. It was purchased by Edwin Smith in the 1862 after it was offered for sale by Mustafa Agha. It is now housed in the New York Academy of Sciences after being donated by his daughter in 1906. This papyrus is said to date from 1550 BC and was taken from the tomb of a physician. The papyrus includes 17 pages with 377 lines on the recto (front) and 5 pages with 92 lines on the verso (back) written with the same hand in a style of Middle Egyptian dating. It was translated by James Henry Breasted, director of the Oriental Institute at the University of Chicago, in 1930. This papyrus, in contrast to the other medical papyri, gives a unique view of Ancient Egyptian medicine since it illustrates the doctor's approach to patient examination to decide on a diagnosis and prognosis before giving the proposed treatment. It is mainly a work which deals with traumatic disorders and it is difficult to identify whether this was a typical general manual for the practitioner aimed at the treatment of daily injuries or whether it was a manual to manage injuries sustained in warfare. Unlike most of the other papyri this one is relatively free of magic and spells. [The transcribed text can be seen at *http://www.reshafim.org.il/ad/egypt/timelines/topics/smithpapyrus.htm*].

This mainly traumatic surgery-oriented treatise is systematically organized in an arrangement of cases, which begin with injuries of the head and proceed downward through the body. The treatment of these injuries is rational and chiefly surgical; there is resort to magic in only one case out of the forty-eight cases preserved. Each case is classified by one of three different verdicts: (1) favorable, (2) uncertain or (3) unfavorable. The third verdict, expressed in the words, "*an ailment not to be treated*" is found in no other Egyptian medical treatise. The Edwin Smith Papyrus opens with eight texts concerning head wounds, followed by nineteen treatments of wounds to the face (forehead, eyebrows, nose, cheeks, temples, mouth and chin), six descriptions of how to deal with injuries to throat and neck, five dealing with collar-bones and arms, and seven for chest complaints.

The Ebers Papyrus was also purchased in Luxor by Edwin Smith in 1862. It was said to have come from a tomb on the West Bank, possibly the same tomb as the Edwin Smith Papyrus. It was said to have been found between the legs of a mummy in the Assassif district of the Theben necropolis. It was subsequently purchased by Georg Ebers in 1872 and eventually found its way to the University Library in Leipzig. In 1875, Ebers published the text in a facsimile with an English-Latin vocabulary and introduction. The papyrus is composed of 110 pages with some further text on the reverse side. It is dated by a passage on the verso to the 9th year of the reign of Amenhotep I (c. 1534 BC). However, Paragraph 856a states that: "*the book of driving wekhedu from all the limbs of a man was found in writings under the two feet of Anubis in Letopolis and was brought to the majesty of the king of Upper and Lower Egypt Den.*" The reference to the Lower Egyptian *Den* is a historic anachronism which suggests an origin closer to the First Dynasty (c. 3000 BC) The text is generally difficult to follow suggesting that it was a compilation from various sources with the scribe not entering remedies and ailments in the correct order. The structure of the papyrus is organized by paragraph, each of which is arranged into blocks addressing specific medical ailments. It deals with remedies of the skin, abdomen and other parts of the body; while the final part deals with surgical procedures, ulcers and tumours. [The transcribed text at *http://www.reshafim.org.il/ad/egypt/timelines/topics/eberspapyrus.htm*].

Paragraphs 1-3 contain magical spells designed to protect from supernatural intervention on diagnosis and treatment. They are immediately followed by a large section on diseases of the stomach (*khet*), with a concentration on intestinal parasites in paragraphs 50-85. Skin diseases, with the remedies prescribed placed in the three categories of irritative, exfoliative, and ulcerative, are featured in paragraphs 90-95 and 104-118. Diseases of the anus, included in a section of the digestive section, are covered in paragraphs 132-164. Up to paragraph 187, the papyrus follows a relatively standardized format of listing prescriptions which are to relieve medical ailments. However, the diseases themselves are often more difficult to translate. Sometimes they take the form of recognizable symptoms such as an obstruction, but often a specific disease term such as *wekhedu* or *aaa* could be found, the meaning of which remain quite obscure. Paragraphs 188-207 comprise "*the book of the stomach*" and show a marked change in style to something which is closer to the Edwin Smith Papyrus.

continues on page 20

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Pneumococcal saccharide conjugated vaccine, adsorbed. Presentation: Each 0.5ml dose of Prevenar contains 2 micrograms of each of the following saccharide serotypes: 4, 9V, 14, 18C, 19F, 23F and 4 micrograms of saccharide serotype 6B. Each saccharide is conjugated to the CRM197 carrier protein and adsorbed on aluminium phosphate. Indications: Immunisation against invasive disease (including sepsis, meningitis, bacteraemic pneumonia, bacteraemia) caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. Dosage and Administration: For intramuscular injection. Infants 2-6 months: Two doses with at least a 1 month interval between doses. A third dose is recommended in the second year of life. Infants 7-11 months: Two doses with at least a 1 month interval between doses. A third dose is recommended in the second year of life. Children 12-23 months: Two doses with at least a 2 month interval between doses. Children 24 months-5 years: one single dose. Contra-indications: Hypersensitivity to any component of the vaccine or to diphtheria toxoid. Warnings and Precautions: Do not administer intravenously. Appropriate treatment must be available in case of anaphylaxis. Impaired immune responsiveness may affect antibody levels. Prevenar does not replace 23-valent polysaccharide vaccine in at risk children ? 2 years of age. Prophylactic antipyretics recommended when vaccinating children with history of seizure disorders, or when vaccinating simultaneously with whole cell pertussis vaccines. Delay vaccination in acute moderate or severe febrile illness. Data are limited on vaccination of children in high-risk groups for invasive pneumococcal disease. Side Effects: Very common: Decreased appetite, vomiting, diarrhoea, injection site reactions (e.g. erythema, induration/swelling, pain/tenderness), fever equal to or over 38 degrees C, irritability, drowsiness, restless sleep. Common: Injection site swelling/induration and erythema larger than 2.4cm, tenderness interfering with movement, fever over 39 degrees C. Uncommon: rash/urticaria. Rare: Seizures including febrile seizures, hypotonic hyporesponsive episode, injection site hypersensitivity reactions (e.g. dermatitis, pruritus, urticaria), hypersensitivity reactions including face oedema, angioneurotic oedema, dyspnoea, bronchospasm, anaphylactic/anaphylactoid reaction including shock. Very rare: Lymphadenopathy localised to the region of the injection site, erythema multiforme. Legal Category: POM Package Quantities: Pack of 1 single-dose vial. Marketing Authorisation Numbers: Pack of 1 (vial): EU/1/00/167/001 Marketing Authorisation Holder: Wyeth-Lederle Vaccines S.A., Rue du Bosquet 15, B-1348 Louvain-la-Neuve, Belgium. For full prescribing information see the Summary of Product Characteristics. Further information may be obtained from: Wyeth (Malta) Sanitas Building, Tower Street, Msida MSD 1824. Telephone: 800 73102 Date of preparation: January 2008prescribing

Malta Institute for Me

www.maltime.co

A focus on excellence in the middle of t

Mission Statement: "to accelerate the diffusion of best evidence-based medical information and to foster interaction and discussion among healthcare providers using the latest information technology".

The Malta Institute for Medical Education (M.I.M.E.) is a new concept for an international teaching institute created to promote postgraduate medical education in Malta. In putting together an international faculty, a team of established local academics have invited international authorities as well as prominent expatriate Maltese lecturers in all medical disciplines to collaborate together. The academic content will include formal didactic courses, but also skills courses, as well as workshops, seminars and masterclasses. M.I.M.E. will also be hosting a virtual academy supporting online training.

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is perceived by its promoters as a cluster of medical knowledge facilities, ciplinary medical, dental, eutical, and paramedical, and it s the f these allied professionals. vices offered by the Institute will not d only to local graduates, but will be l to countries in the Mediterranean

Strategically, Malta is well placed as a location for this centre. The proposed Institute will be a prestigious academic forum bridging Southern Europe and North Africa. The fact that it will be located in an English-speaking country which is safe, within the European Union and therefore politically and economically stable, with a wealth of history and culture, and enjoying an excellent maritime climate, renders it all the more attractive and unique.

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ic Gastroenterology Course	25th - 27th Sep 2008
Vertigo Course; management and core skills	15th – 17th October 2008
ranean Council Burns Course	24th - 25th Oct 2008
ranean Grown Up Congenital Heart Disease Course	4th - 5th Dec 2008

Vacancy

Family Doctor in the South with 40 years experience in family medicine, locally and abroad, planning to retire in the near future invites a young family doctor to join the practice with a view to taking over all the work.

Kindly apply to Professional Services Centre, Guzi Cutajar Str., Dingli or send an e-mail to jobs@gpclinic.net

All applications will be dealt with in strict confidence.

Volunteers

Dear colleagues,

This year being the 150th anniversary of Our Lady's apparitions in Lourdes, AVL (Assocjazzjoni Voluntarji Lourdes), of which I, at present, am the medical director, is organizing a pilgrimage for Maltese and Gozitan sick children (ages 0 -14 years) between the 22nd June and the 27th June 2008. The Maltese children will be joining a pilgrimage of over 4,000 children organized by the Italian Lourdes organization UNITALSI.

AVL needs medical volunteers, preferably with some Pediatric experience, to accompany these kids to Lourdes. The price would be in the region of 550 Euro, all inclusive. Anyone interested please contact me on 99492349, or Dr. Godfrey Agius on 79492444, or Mrs. Cecilia Sultana on 99424581.

Please help us make this pilgrimage be an experience of a lifetime to these sick kids.

Joseph Grech-Attard MD

Pharmacy of Your Choice

Change and Innovation in Community Pharmacy – The Phased Implementation of the Pilot Study

by **Mary Ann Sant Fournier** *BPharm MPhil*
President, Malta Chamber of Pharmacists
Professional centre, Sliema Road, Gzira
Website: www.synapse.net.mt/mcp/
Email: spizjar@waldonet.net.mt

The phased implementation of the Pharmacy Of Your Choice (POYC) pilot study was introduced in December 2007, in 2 private community pharmacies in the Gharghur area (approximately 550 patients). This was followed by Mgarr (1 community pharmacy – approximately 600 patients) and Mellieha (3 community pharmacies – approximately 1500 patients) in January 2008 and Naxxar in February. The remaining phases of the pilot area will follow in the latter part of March and shall include Qawra and Bugibba. The pilot shall be concluded with the inclusion of St Paul's Bay and finally, Mosta.

With regard to the national roll-out, patient registration (Figure 1) in the localities served by the Rabat health centre, including Attard, Bahrija, Dingli, Mtarfa and Rabat, and in those served by the Gzira Health Centre, including Gzira, Msida, Paceville, Pembroke, St. Andrew's, San Gwann, Sliema and Swieqi, was launched in January 2008 and shall last till the 15th March 2008.

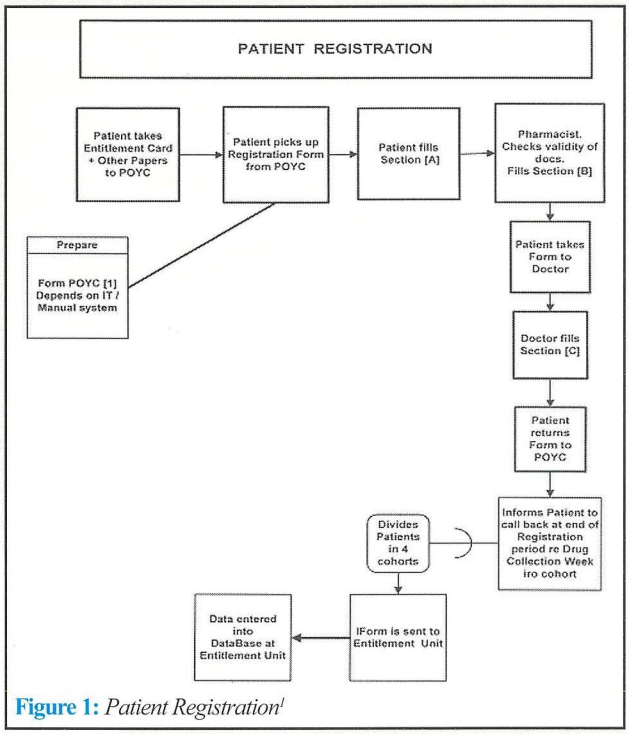


Figure 1: *Patient Registration*[1]

It is expected that all patients in Malta would have registered with their chosen pharmacy by end 2008 after which the scheme will be extended to Gozo.

The Pilot Computer System – *a virtual private network*

The computer system which is being employed during the pilot study is based on a virtual private network (VPN). Figure 2 presents a concise logistic plan of the system in place at present:

1. The patient is electronically registered at a pharmacy of their choice
2. This data becomes available in the national entitlement database
3. The pharmacist dispenses the medicines keying in information at the front end of the system
4. These are registered in the Stock Transfer System (STS)
5. The STS program sends all information to the national entitlement database and stocks are deducted accordingly.

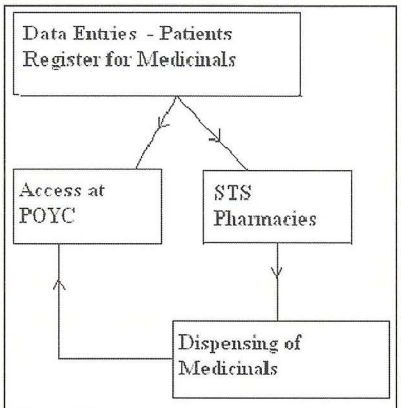


Figure 2: *Concise Logistic Plan Of The POYC Pilot System*
Note: A MITTS database system integrated with an Access Dimensions financial package

In a relatively short time, the members of the MITTS and Standing Advisory Committee (SAC) worked intensively to design, install and test the system. An on-site and one-to-one approach at each pilot pharmacy has been adopted. The computerization of the pharmacies is being achieved through an 'e-service' level agreement with private service providers, typically comprising a computer and label printer and including repair or replacement on an agreed reduced on-site response time. Data entry in the construction of the national entitlement database and the medication records remains one of the mainstays of the project. This has had to address the conversion of the many trade names which are still being used by prescribers in lieu of generic names of medicinal products at NHS level. The knowledge and support of the pharmacists and other members of the Pharmaceutical profession in this regard has proven to be crucial. The human resource involved in data entry and system administrators are mainly pharmacy technicians.

The way forward for full computerisation of community pharmacy has been agreed upon and is expected to reap benefits in the goals for primary health care. As expected, the uptake by the pharmacists has been extremely encouraging and highly professional.

The Chamber looks forward to the opening of new ICT venues which are expected to enhance intra-professional relationships with hospital based colleagues and inter-professionally, especially with family doctors, for true effective seamless care in the community.

The Central Processing Unit (CPU) – *supporting community pharmacists in the implementation of the POYC*

The Central Processing Unit was established in the Directorate for Special Initiatives of the Health Care Services Division of the Ministry of Health, the Elderly and Community Care with the following remit[2]:

- Provide ongoing technical support to pharmacists practicing in private community pharmacies;
- Maintain the individual patient entitlement database;
- Determine stocks of pharmaceuticals required by private community pharmacies;
- Order, prepare and distribute stocks required by private community pharmacies;
- Manage the stock control IT system.

At present an exercise is underway to redeploy necessary staff from the Health Division to achieve the necessary human resource complement to reach the objectives of the CPU and the POYC.

A main objective is the timely delivery of the stocks of required medicines, in quantities and packaging which diminish to the least possible the work of the community pharmacists in the preparation of the different entitlements of their patients, so that their time is

continues on page 28

Introducing Panadol Sinus

Powerful relief from Sinus Pain & Congestion

Research in Children

by **Pierre Mallia** *MD MPhil PhD MRCP FRCGP*
Associate Professor of Family Medicine and Patient's Rights
Department of Family Medicine, Medical School
University of Malta

The Centre for Bioethics and Patient Advocacy has been taking part in the European Forum for Good Clinical Practice (EFGCP)'s formulation of guidelines for implementing Directive 2001/20/EC[1] relating to good clinical practice in the conduct of clinical trials on human subjects. The document produced by this group focused on clinical trials in children and their protection thereof. As clinical trials become more important and common, a harmonization of the application of this directive across Europe was deemed important.

"Children are not small adults and there is a need to carry out specific trials that cannot be performed in adults."[2] Ethics committees need paediatric expertise as the lack of competence of children to give informed consent renders this group a vulnerable population. In particular parents are prone to accept their children participating in a trial upon the suggestion of the health care team. The lack of legal ability to consent has therefore also implications on the design, analysis and the choice of comparators used in trials. There is a need for clinical trials in children, especially because many drugs given to them are off-label. Moreover trials may be specific to this population, such as vaccinations.

The Declaration of Helsinki states that, "When a subject deemed legally incompetent, such as a minor child, is able to give assent to decision about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative."[3] This implies that enough information must be given to the child by an experienced professional, which the child is able to assimilate and understand. Article 4 of the Clinical Trials Directive stipulates therefore "the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator."[2]

As the child however is only capable of giving assent and not informed consent, one still needs to follow the five conditions[4,5] to obtain valid consent from the legal representative of the child. Sufficient time to consider the risks and benefits should be allowed for.[2] The document divides children into three age groups. Those under three years of age cannot give realistic assent whilst those over three are thought to understand some form of altruism. As the child gets older, children may be able to understand and evaluate the risks and benefits of the research, and their expression must therefore be taken into account. The third group, adolescents, proves most difficult. Sometimes there can be situations in which confidentiality is at stake – some EU states advice discretion and professional secrecy vis-sa-vis parents when dealing with this group. Obtaining consent from parents becomes difficult, if legally required, when assent is available form the adolescent, who is technically still considered a child under the legal guardianship of the parents. Conversely, "when the child is legally emancipated, i.e. ceases to be a minor, informed consent must be sought directly from the individual and as soon as possible".[2]

The Clinical Trials Directive requires the need for ethics committees to have paediatric expertise to give advice in the clinical, ethical and psychosocial problems in the field of paediatrics, which differ of course from the usual clinical trials in adults. This may be a paediatrician experienced in paediatric research and trials, but also a paediatric pharmacologist, paediatric nurse, paediatric ethicist or psychologist. If the ethics committee is not in charge of scientific review according to national law, it should make sure that adequate peer review by experts in the field has taken place – for example that the trial uses age-appropriate formulations of the medicinal product, or that appropriate amounts of blood are drawn, where this is necessary, considering that the volume of blood to be drawn is over and above that for the normal hospital stay. An amount not more that 1.2 ml has been suggested for children under three, especially babies.

Equipoise is important when considering a control group or the use of a placebo. The physician must be morally certain that the child is not better off not participating in the trial. Equipoise may be waived however when the trial does not involve control groups, for example post-marketing surveillance studies. It has also been suggested that research on certain drugs, following of course the scientific advice given by the professionals mentioned, should be offered only on premises where appropriate "rescue treatment and escape procedures" are available, should a serious harm occur.[2]

Of course an obvious requirement is that physical and emotional pain should be prevented as much as possible. To do this however requires appropriate monitoring on a regular basis according to guidelines and validated scales, particularly in pre-term, newborn and other children who cannot express themselves. Effective treatment in relation to the intensity of pain should be administered and reviewed regularly. Repeated blood sampling and the insertion of indwelling catheters are all sources of pain, and available pharmacokinetic data from population studies may reduce the number of samples in each child.

Risk assessment is crucial when assessing trials. In children particularly, besides the physical risks, one must consider the psychological or social risks, which may be immediate or delayed and which may vary according to age. Absenteeism from school may be a small issue to the health care team, but may have a large impact over a stretched period of time. It is often the case that the research is spread over the availability of the research team and not of the child's timetable. Ethics committees may intervene when it is deemed that the particular age group

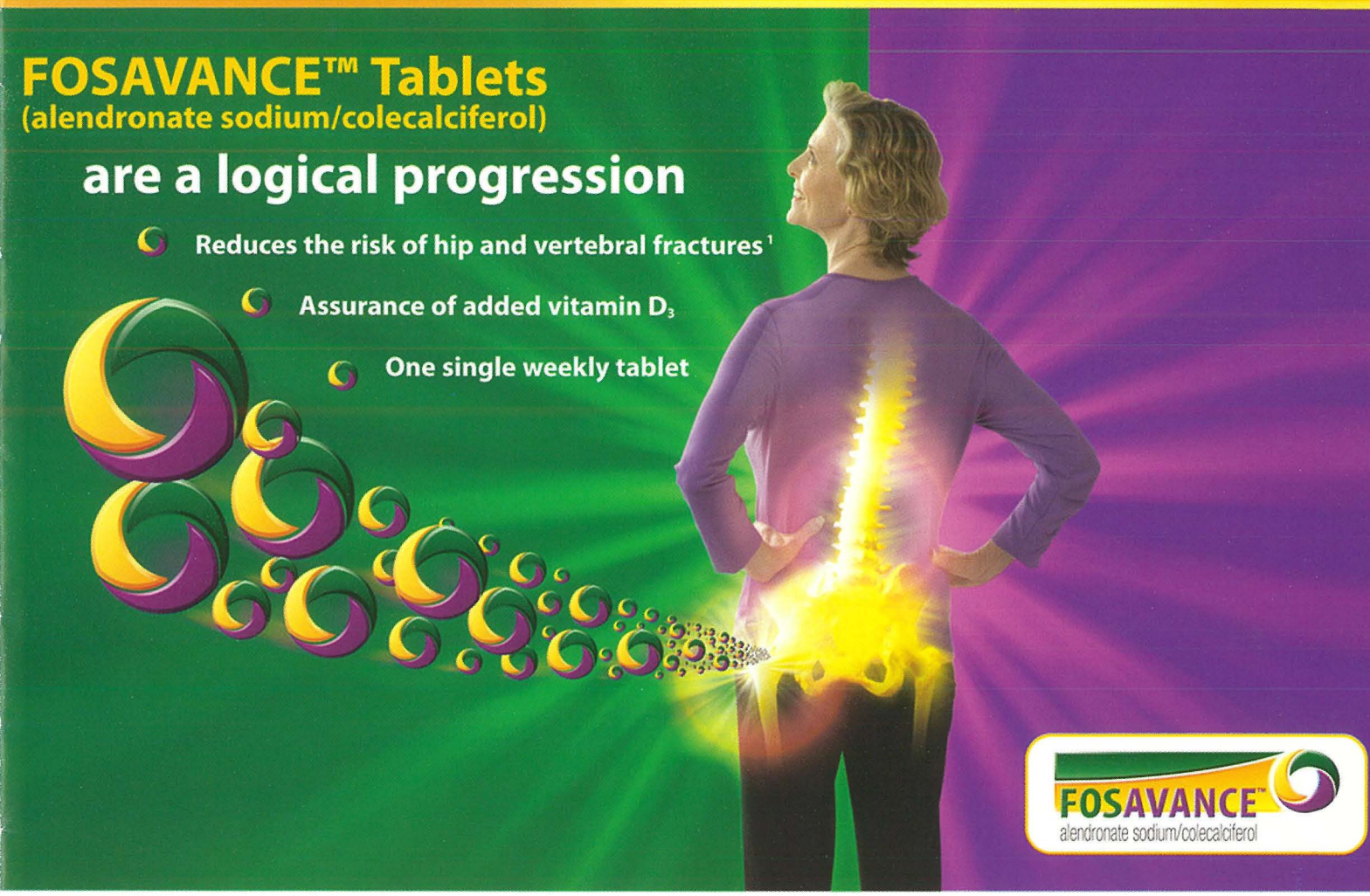
continues on page 20

TREATING YOUR POST-MENOPAUSAL OSTEOPOROSIS PATIENTS

FOSAVANCE™ Tablets
(alendronate sodium/colecalciferol)

are a logical progression

- Reduces the risk of hip and vertebral fractures[1]
- Assurance of added vitamin D_3
- One single weekly tablet



FOSAVANCE™
alendronate sodium/colecalciferol

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 may increase the magnitude of hypercalcaemia and/or hypercalciuria. Patients with malabsorption may not adequately absorb vitamin D. *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.

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
'Fosavance' Tablets 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
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

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.

MSD
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

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Research in Children

continued from page 18

may be adversely affected, and that appropriate arrangements, such as the use of holidays, are used to bring children to the facilities, unless one is dealing with hospitalised children. It is all too easy to instruct parents that they must then continue to bring in the child once a week (when this may not have been adequately expressed in the informed consent process). Parents are usually the first to express concern about how much time is lost from school.

However the risk-benefit analysis may evolve over time, especially where the safety of the drug is concerned, and this must be continuous evaluated, with the provision of being able to stop the study if necessary. There are various protocols and tables of assessing what are minimal risks, and which are major ones. These must be presented by the trial sponsors and need to be evaluated by the Ethics Committee, which usually tries to ascertain that risks are minimal as well as the burden, and that the research has the aim of providing significant improvements in the scientific understanding of the condition or disease, which are able to provide benefit to the participant of the trial and other persons of the same age category.

More tricky are phase one trials, in which healthy volunteers are used. Healthy children must be used in order to understand the pharmacokinetics and pharmacodynamics of a drug, without the interference of the disease process. Phase one involves small numbers, usually in the order of tens; but still, assessing and imparting information of risk may be more difficult, unless one produces prior evidence of adult studies, or at least animal studies. This may not be necessary where the aim is to find age-appropriate dosages or for trials for vaccines. Whenever possible, it is suggested that older children should be considered for inclusion before younger ones, although the document[2] does not give particular reasons for this, other than the impression that the younger the child, the more vulnerable they are, and probably the more prone to risks. This may reduce the impact on future tests on younger children.

Finally the directive admonishes researchers performing research in non-EU countries, to strictly follow the same guidelines and GCP standards that are required within the EU. Indeed this is not only about patient rights, but at the end of the day, also about the scientific validity of the trial, for research which is not up to Good Clinical Practice standards has been found not to be scientifically valid.

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2. European Commission. Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population - Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.
3. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Revision 2004. Available at: http://www.wma.net/e/policy/b3.htm
4. Mallia P. Obtaining Informed Consent – Part I. *The Synapse Magazine* 2006;6:12.
5. Mallia P. Obtaining Informed Consent – Part II. *The Synapse Magazine* 2007;1:8.

Ancient Egyptian Medicine

Part IV [1] – Medical Papyri

continued from page 12

Only paragraph 188 has a title, though all of the paragraphs include the phrase: "*if you examine a man with a ...*" a characteristic which denotes its similarity to the Edwin Smith Papyrus. From this point, a declaration of the diagnosis, but no prognosis can be found. After paragraph 207, the text reverts to its original style, with a short treatise on the heart (Paragraphs 208-241). Paragraphs 242-247 contain remedies which are reputed to have been made and used personally by various gods. Only in paragraph 247, contained within the above mentioned section and relating to Isis' creation of a remedy for an illness in Ra's head, is a specific diagnosis mentioned. The following section continues with diseases of the head, but without reference to the use of remedies by the gods. Paragraph 250 contains a famous passage concerning the treatment of migraines. The sequence is interrupted in paragraph 251 with the focus placed on a drug rather than an illness. Most likely an extract from pharmacopoeia, the paragraph begins: "*Knowledge of what is made from degem (most likely a ricinous plant yielding a form of castor oil), as something found in ancient writings and as something useful to man.*" Paragraphs 261-283 are concerned with the regular flow of urine and are followed by remedies "*to cause the heart to receive bread.*" Paragraphs 305-335 contain remedies for various forms of coughs as well as the *genew* disease. The remainder of the text goes on to discuss medical conditions concerning hair (paragraphs 437-476), traumatic injuries such as burns and flesh wounds (paragraphs 482-529), and diseases of the extremities such as toes, fingers and legs. Paragraphs 627-696 are concerned with the relaxation or strengthening of the *metu*. The exact meaning of *metu* is confusing and could be alternatively translated as either meaning hollow vessels or muscles tissue. The papyrus continues by featuring diseases of the tongue (paragraphs 697-704), dermatological conditions (paragraphs 708-721), dental conditions (paragraphs 739-750), diseases of the ear, nose, and throat (paragraphs 761-781), and gynecological conditions (paragraphs 783-839).

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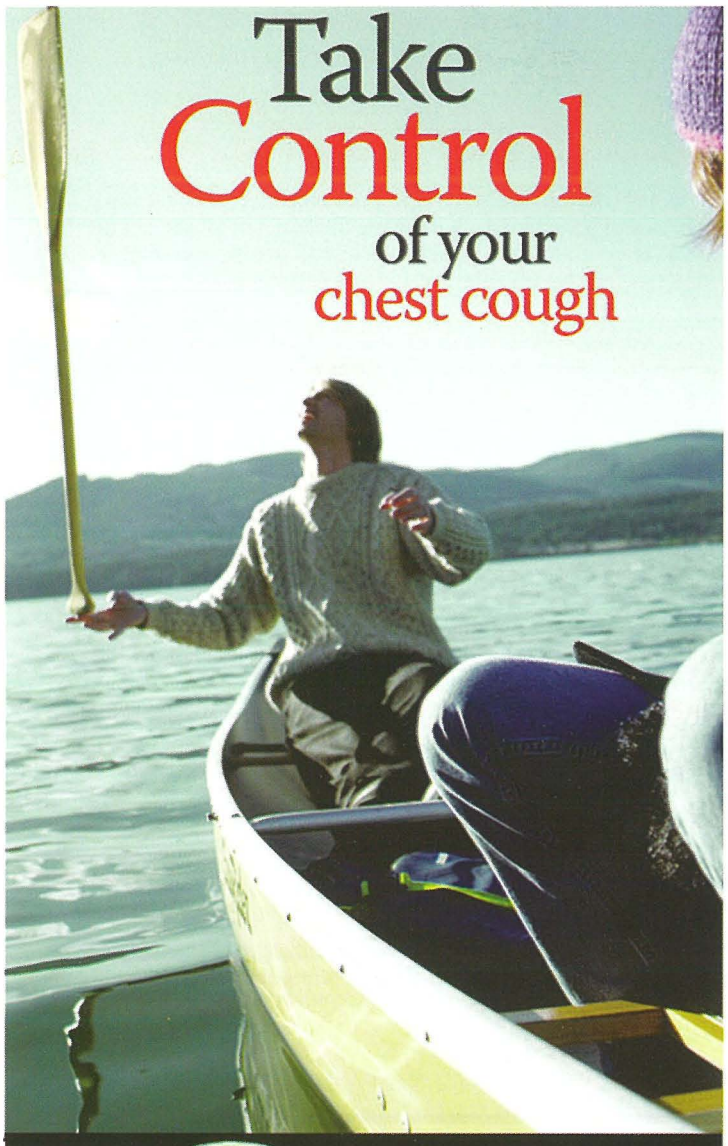

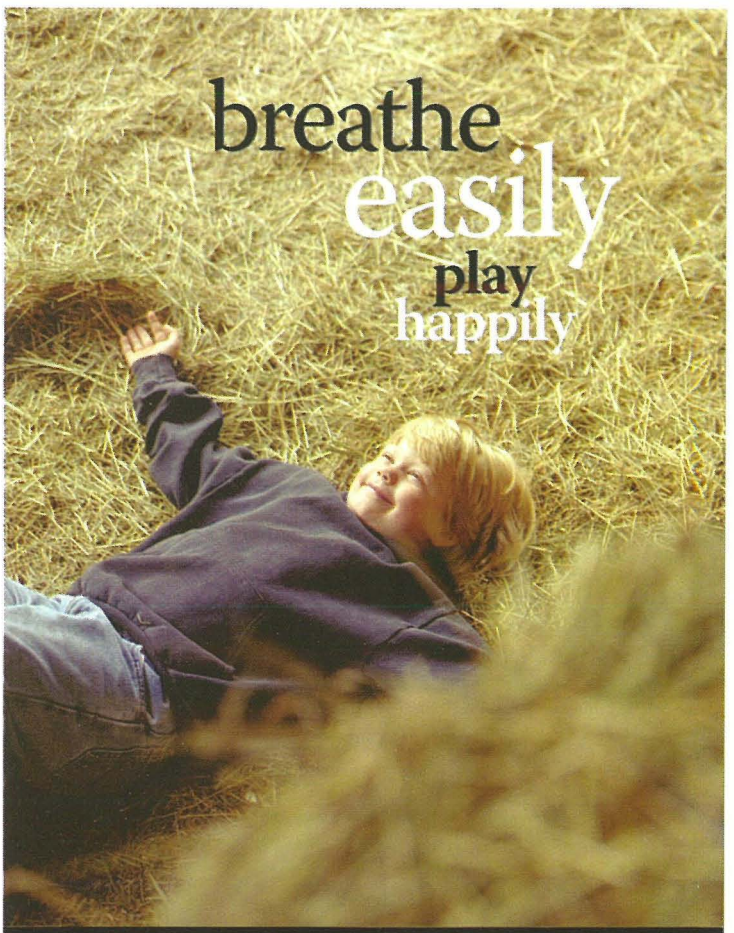

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MT_CAR_08_02_01

A Passion for Life in Mini

by **Marika Azzopardi**

They consume up to 25% of all crops and grains gathered worldwide and can easily spoil all the rest. They occupy every niche of our planet and can associate themselves intimately with most other organisms. No, they are not aliens trying to take the world over. They already own the world – they are insects. They are also the territory of Dr Paul Gatt, consultant dermatologist by profession and entomologist by passion.

Studying an organism which can span the grandiose width of 3mm or even less...a microscopic 1mm, is not something most of us would take up gladly. Yet Dr Gatt claims this was his fascination from childhood.
"I used to spend many happy hours pottering about in a field near my home seeking them out – turning a stone here, looking at a flower there – not understanding much, but still marvelling at their number, beauty and endless variety of form and colour as they quietly went about their daily lives."

Great things begin in such simple manners that are tinged by inbred inquisitiveness. Although the study of insects might not sound like a big deal, there is more to insects than we credit them for. Dr Gatt explains the widespread influence they have over our civilisations. "For one thing insects are extremely adaptable, with some species living in glaciers, thermal springs, and even crude oil! Their sheer numbers provide food for countless birds, fish and other forms of life. They are vital elements of the food chain when we consider their importance as pollinators of crops and grains that provide the bulk of the world's food. Insects are equally vital in decomposing decaying matter without which the earth would be littered with dung and dead bodies. And, from a purely anthropocentric point of view, they are responsible for spoiling much of the earth's crops and grain and costing millions of lives in deaths from insect-borne disease." Not very exhilarating news!

Considering the fact that only one million species are known to scientists and yet a staggering seven million are estimated as still waiting to be discovered, Dr Gatt was surely right into entering an area of research with much potential.

Dr Gatt out in the field in the jungles of French Guyana

Starting off from the 'large' specimens the likes of butterflies, beetles and bees, insects that titillate the curiosity of just about any average child, his research took him to smaller and smaller insects which became definitely harder to study.

"I must admit that joining the Natural History Society of Malta, way back as a youth, helped me form my interest better. It was there that I met wonderful naturalists and teachers – people like Guido and Edwin Lanfranco, Patrick Schembri, Joe Cilia and Anthony Valletta – who inspired me greatly. The enthusiasm at the society was infectious, and a number of us – Albert Bezzina, Noel Camilleri, Carmelo Aquilina (all of them medical doctors now), James and Stephen Schembri, Louis Cassar, David Mifsud and Guido Bonett met during the Society meetings and became life-long friends."

"I owe my first beginnings in entomology to Joe Cilia who patiently and enthusiastically endured the company of a 13 year old boy who never seemed to stop asking questions! I used to accompany him on collecting trips, and it was he who taught me the initial field and curatorial skills necessary to build up an insect collection. Once a week I used to visit him at his home, and he would give me the names of the insects I had collected, with explanations of how they lived and what they did. I marvelled at the diversity of insect life even in a small place like Malta."

Today he is practically the only active medical authority in entomology in Malta and whilst he admits he would have taken up entomology had he had the opportunity to do so, he does find that entomology aids him in his work related to the human skin.

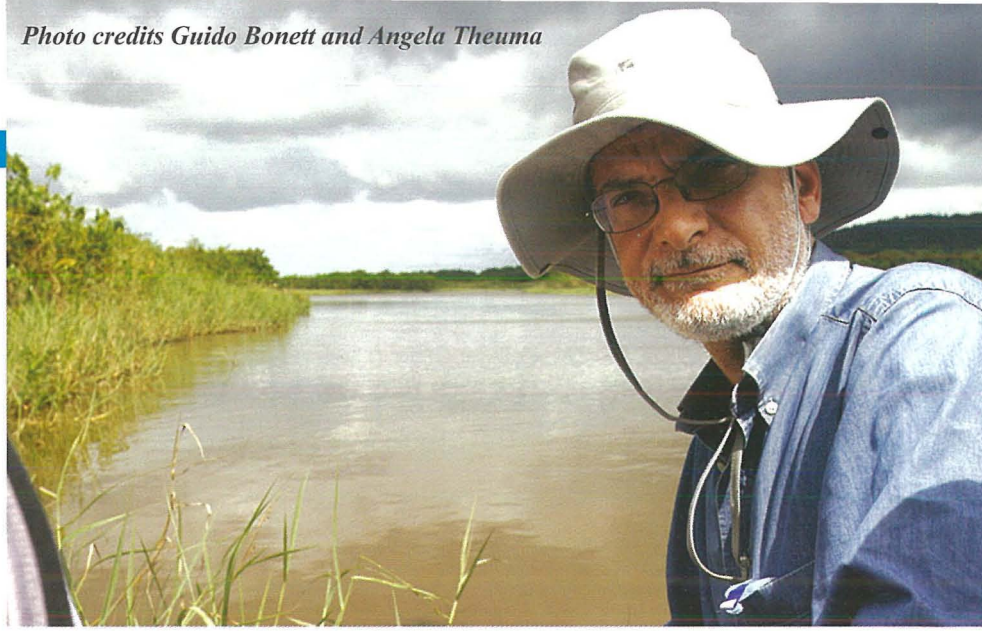
"I can understand better the skin diseases and internal illnesses caused by insects. My travels have aided me in this respect and whilst I began by researching the Mediterranean basin initially, I did move out to diverse countries such as South America or Ethiopia to experience insect life there as well." Training to observe minute creatures also helps aid his eyes in detecting subtle skin manifestations that can indicate disease.

Meeting Martin Ebejer, a fellow physician who had just returned to Malta from the UK – at that time already a highly skilled and experienced dipterist – was tantamount to consolidating his interest in entomology. He frankly admits, "Were it not for his influence and enthusiasm I doubt if I would have ever returned to entomology, an interest I had to shelve because of my specialisation in dermatology. Martin introduced me to the rigours of taxonomy and generously shared his literature and contacts with international experts and museums with me. John C. Deeming of the National Museum, Cardiff introduced me to a family of tiny flies – Sphaeroceridae – which would occupy most of my interest for the coming years. What began as a simple hobby transformed itself into a serious and rewarding study, and I found myself plunging deeper into diptera morphology and systematics, which interest me particularly for their astounding biodiversity."

ature

Dr Gatt at the microscope

Photo credits Guido Bonett and Angela Theuma



He kicked off his studies by honing in on Maltese fauna but then broadened his experience by collecting first in the UK - where the fauna was well known - and later in many places around the Mediterranean basin, including North Africa. "Fauna of North Africa is also very poorly known, and more recently I also experienced the tropical rainforests of French Guyana. With Martin Ebejer's encouragement, I began compiling my findings which included those related to four species new to science from Malta and elsewhere, and publishing them in international peer reviewed journals. My collaboration with foreign specialists also resulted in two previously unknown species being named after me - Platypalpus gatti and Tethina gatti."

What about Malta's urbanisation – is it destroying insect existence on a local level? "A lot is fast disappearing, but the insects I study are minute creatures which you wouldn't see easily with the naked eye. You have to know where to find them by knowing what they do. And pockets of life are still to be found fortunately teeming with insect life that interests me." It is around these pockets of life that Dr Gatt collects specimens of Diptera in order to study them better, first by mounting, dissecting and scrutinising them, then by documenting their structure. It is a process which Dr Gatt admits can be extremely taxing, time consuming and tedious.

And the fascination continues. Certainly Dr Gatt is a well of information about a world we generally ignore and at best merely acknowledge. The papers Dr Gatt has written may not be interesting to many except perhaps a handful of similarly inclined scientists and he admits, "I do all my entomology in my limited spare time, and my only regret is that I will probably never finish off what I have already started." The time is probably ripe for more scientists of this calibre to delve deeper into nature's uncharted mysteries.

Prediction of falls among the elderly at risk – Part I

by **Melanie Muscat** *BSc Physiotherapy, SRP Physiotherapist*

Falls and falls prevention among the elderly population has become a major concern to health organizations and governments globally.[1] Falls are among the most common and serious problems facing elderly persons and their health care providers.[2]

Facts

Falling is associated with considerable mortality, morbidity, reduced function and pre-mature nursing home admissions.[2] 30% of persons over 65 years old and 50% of persons over 80 experience one fall a year. 90% of hip fractures amongst this population are attributed to falls.[3] Hip fractures lead to serious disability – 60% will need some form of assistance at home to carry out simple daily activities such as dinner preparation and walking. About 20% are ultimately admitted into nursing homes.[4]

However, not all falls are considered to be equally important. Falls that count are those that occur during daily activities, where there is no recall of preceding events or there is a loss of consciousness, when injury was sustained, long lie and subsequent loss of confidence.[5]

With the exception of syncopal episodes, most falls are multifactorial in origin, resulting from a combination of intrinsic and extrinsic factors (Figure 1). However musculoskeletal weakness amongst the older population is the major contributing factor followed very closely by impaired balance. These physiological changes are not a direct effect of ageing but due to physical inactivity that comes along with the lifestyle adaptations of this population. Worth noticing is the fact that women have a higher incidence of falls as compared to men, the most likely factor being the increased use of psychotropic drugs amongst this gender, as well as the ratio of weight to lower limb strength, and living alone.[5]

Intrinsic Factors	Extrinsic Factors
Age Musculoskeletal weakness Gait Instability Medication Vision Chronic illness	Home Hazards Public environment Footwear

Source: Kings College Hospital (UK)

Figure 1: *Intrinsic and Extrinsic risk factors*

How to predict falls among the elderly

During her conference held in Sydney Dr. Jacquie Close, a prominent researcher in the field related to falls, highlighted the most useful clinical indicators used to identify whether an individual is likely of sustaining a fall in the future. These indicators lie in 4 simple questions:

- **Is the patient over the age of 65 years?**
- **Has the patient suffered more than one fall in the last 6 months?**
- **Was the falls indoors?**
- **Is the patient on more than 4 medications?**

Three out of four affirmations of the above would require **further investigation** as the patient is most likely to suffer another fall in the next 3 months with serious debilitating effects. The American Geriatrics Society (AGS), and the British Geriatric Society (BGS) guideline recommends the Timed Up and Go Test - TUGT as an effective screening tool for identifying older people at increased risk of falls.[6] TUGT has been validated and recommended as a simple screening tool and may be used in parallel by general practitioners to identify those at risk.

1. Stand up from chair with arm rest (standard height 43 cm)
2. Cover a distance of 2.5 – 3 meters, at patients' own pace
3. Turn around and sit back again on chair
4. The target time is 10 seconds for community dwellers and 15 seconds for more frail individuals

Figure 2: *Screening Test – Timed Up and Go*

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Melanie Muscat is a physiotherapist working at the Live Life Wellness Centre for Active Adults, Prince of Wales Apartments, Manuel Dimech Street, Sliema. She can be contacted on livelife@infonetcom.mt. Alternatively you may visit: www.livelife.com.mt

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Imaging Pyelonephritis - Part I

continued from page 2

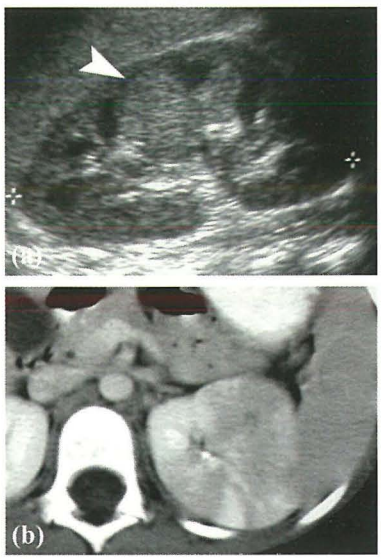

Figure 4. (a) *US scan demonstrates a geographic, slightly lobulated "mass" (arrowhead) in the midpole of the left kidney, a finding that is suspicious for a solid tumour.* **(b)** *CT scan shows multifocal regions of diminished enhancement that extend to the periphery of the kidney, findings consistent with interstitial nephritis.*

US findings seen in pyelonephritis include congenital anomalies and a variety of changes in the renal parenchyma such as hydronephrosis, renal enlargement, loss of renal sinus fat due to oedema, changes in echogenicity due to both oedema (hypoechoic) or haemorrhage (hyperechoic) (Figure 2a), loss of corticomedullary differentiation, abscess formation, and areas of hypoperfusion (visible with power Doppler interrogation) (Figure 2b). Even when positive US findings are observed, US is limited in the definitive differentiation of calcification from intraparenchymal or collecting system gas, identification of perinephric extension of infection, and visualization of small microabscesses that are common in early acute infections (Figure 3). Occasionally, areas of abnormal echogenicity can have a tumour-like appearance (Figure 4). However, taking the clinical picture into consideration and if necessary short term US follow-up will resolve the issue in most cases.

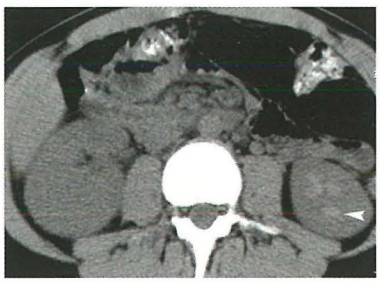

Figure 5. *Unenhanced CT scan from a clinically documented case of acute bacterial pyelonephritis shows asymmetric enlargement and absence of the pyramids of the right kidney. The normal left kidney shows preserved pyramids [arrow].*

Unenhanced CT is excellent for identifying urinary tract gas, calculi, haemorrhage, renal enlargement, inflammatory masses, and obstruction (Figure 5). Involved regions occasionally appear with lower attenuation related to oedema; less frequently, they have pockets of higher attenuation that are thought to represent haemorrhage (Figure 6).

When multiple round, peripheral hypoattenuation renal lesions are seen in the clinical setting of pyelonephritis, hematogenous seeding should be considered (Figure 7). Blood and urine cultures that grow organisms associated with skin or oral flora, such as *Staphylococcus* or *Streptococcus* species, support the hypothesis of hematogenous infection. However, when the lesions within the kidney or coalesce, differentiating between ascending and hematogenous infection may not be possible. Occasionally, these CT findings are identified in the absence of clinically suspected pyelonephritis and are mistaken for multiple neoplastic masses.

In addition to detecting and diagnosing nephritis more reliably, CT can monitor nephritis more accurately should the need arise (eg in patient's not responding to treatment). However, follow-up is rarely required, as most uncomplicated cases will respond to first line treatment.

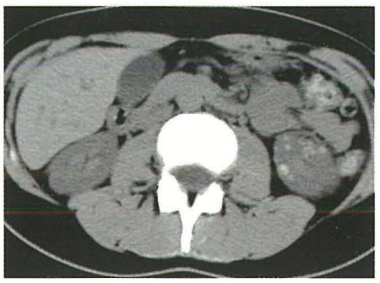

Figure 6. *Unenhanced CT scan demonstrates multiple, scattered, round and oval hyperattenuation foci within the left kidney, findings indicative of hemorrhagic acute bacterial pyelonephritis.*

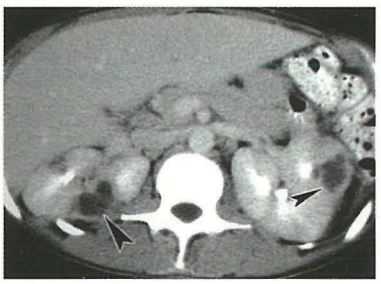

Figure 7. *Acute bacterial pyelonephritis caused by haematologic seeding in a patient with* Staphylococcus aureus *endocarditis. CT scan demonstrates peripheral low-attenuation lesions (arrowheads) that are maturing into small abscess cavities. In such cases, blood and urine cultures grow the same organism.*

The next article will deal with complicated and less common types of pyelonephritis including xanthogranulomatous pyelonephritis, and tuberculosis, where CT is of even greater value.

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Patients with impaired renal function (creatinine clearance less than 50 ml/min or serum creatinine of more than 300 micromol/l) should be treated with half of the normal dose. *Skin infections* - The likely duration of treatment for Tinea pedis, Tinea corporis and Tinea cruris is 2 to 4 weeks. For Tinea pedis (interdigital, plantar/moccasin-type): recommended treatment periods may be up to 6 weeks. Complete disappearance of the symptoms of the infection may not occur until several weeks after mycological cure. *Onychomycosis* - In most patients the duration of successful treatment is 6 to 12 weeks. Fingernail onychomycosis - In most cases 6 weeks' treatment is sufficient in fingernail onychomycosis. Toenail onychomycosis - In most cases 12 weeks' treatment is sufficient in toenail onychomycosis although a few patients may require treatment up to 6 months. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required. Complete resolution of signs and symptoms of infection may not occur until several weeks after mycological cure and is only seen several months after stopping treatment, which is the time for growth of a healthy nail. *Children and adolescents (< 18 years)* - There is limited experience with oral terbinafine in children and adolescents and therefore its use is not recommended. *Use in elderly* - There is no evidence to suggest that elderly patients require different dosages. *Contra-indications:* Hypersensitivity to terbinafine or to any of the excipients. Severe renal impairment. Severe hepatic impairment. **Special warnings and precautions for use:** Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within two months of starting treatment. If a patient presents with signs or symptoms suggestive of liver dysfunction such as pruritis, unexplained persistent nausea, anorexia or tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine, or pale stools, hepatic origin should be verified and terbinafine therapy should be discontinued. Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine can be reduced by 50%. Therapeutic use of terbinafine in patients with chronic or active liver disease has not been studied in prospective clinical trials, and therefore cannot be recommended. Terbinafine should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported. Patients on terbinafine who develop a high fever or sore throat should be examined due to possible haematological reactions. Terbinafine is a potent inhibitor of the isoenzyme CYP2D6, which should be taken into consideration if terbinafine is combined with medicinal products metabolised by this isoenzyme. Dose adjustments may be necessary. **Interactions with other medicinal products and other forms of interaction:** The plasma clearance of terbinafine may be accelerated by active substances which induce metabolism (such as rifampicin) and may be inhibited by active substances which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such active substances is required, it may be necessary to adjust the dose of terbinafine accordingly. In vitro studies have shown that terbinafine inhibits the CYP2D6 mediated metabolism. For this reason, it is important to monitor patients who are simultaneously treated with active substances that are mainly metabolised by this enzyme, such as tricyclic antidepressants, beta-blockers, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors Type B if the co-administered drugs have a narrow therapeutic index. Other in vitro and clinical studies suggest that terbinafine shows negligible potential to inhibit or induce the clearance of active substances that are metabolised via other cytochrome P450 enzymes (e.g. ciclosporin, tolbutamine, terfenadine, triazolam, oral contraceptives). Some cases of menstrual disturbances such as breakthrough bleeding and irregular cycle in patients taking terbinafine concomitantly with oral contraceptives have been reported. **Pregnancy and Lactation:** Foetal toxicity and fertility studies in animals suggest no undesirable effects. **Pregnancy** - There is no clinical experience with terbinafine in pregnant women. Terbinafine should not be administered during pregnancy unless clearly necessary. **Lactation** - Terbinafine is excreted in breast milk and therefore, nursing mothers should not be given terbinafine whilst breast feeding. Breast-feeding should be discontinued before starting the treatment with terbinafine tablets. **Effects on ability to drive and use machines:** Terbinafine has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** The adverse reactions are usually mild to moderate and transient. Blood and lymphatic system disorders - Very rare (<1/10,000 inclusive isolated reports): Haematological disturbances such as neutropenia, agranulocytosis and thrombocytopenia. Immune system disorders - Very rare (< 1/10,000): Manifestation or aggravation of cutaneous or systemic lupus erythematosus. Very rare (< 1/10,000 including isolated reports): Anaphylactic reactions. Psychiatric disorders - Very rare (<1/10,000 including isolated reports): Psychiatric disturbances such as depression and anxiety. Nervous system disorders - Common (>1/100, <1/10): Headache. Gastrointestinal disorders - Common (>1/100 and <1/10): Gastrointestinal symptoms (feeling of fullnes, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea). Uncommon (>1/1000 and <1/100): Taste disturbances, including loss of taste, that usually revert several weeks after withdrawal of the active substance. Isolated cases of persistent taste disturbances have been reported. In very few severe cases, a reduced intake of food causing significant loss of weight has been seen. Hepatobiliary disorders - Rare (>1/10,000 and <1/1000): Hepatobiliary dysfunction (primarily of cholestatic type). Very rare (<1/10,000 inclusive isolated reports): Severe hepatic failure. Skin and subcutaneous tissue disorders - Common (>1/100 and <1/10): Non-serious skin reactions (rash, urticaria). Rare (>1/10.000 and <1/1000): Severe skin reactions (e.g. Stevens-Johnsons syndrome, toxic epidermal necrolysis, photosensitivity) and anaphylactoid reactions (incl. angioedema). If progressive rash occurs, the treatment with terbinafine should be discontinued. Very rare (<1/10,000 including isolated reports): Exacerbation of psoriasis, loss of hair. Musculoskeletal and connective tissue disorders - Rare (>1/10,000 and <1/1000): Arthralgia and myalgia. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions. **Overdose** - Few cases of overdose (up to 5 g) have been reported. The symptoms are headache, nausea, epigastric pain and dizziness. The recommended treatment is elimination of the active substance, primarily by use of active charcoal and symptomatic treatment. **Marketing Authorisation Holder:** Actavis Ltd. B16, Bulebel Industrial Estate, Zejtun, ZTN 08. Malta.

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Change and Innovation in Community Pharmacy – The Phased Implementation of the Pilot Study

continued from page 16

dedicated to their professional interventions. The introduction of automation at the CPU is, for example, a priority in this regard. Another objective is to reduce the environmental impact of pharmaceutical packaging waste.

Extending the pilot study and introducing registration in the first phase of the national roll-out

In January 2008 an important POYC meeting was held by the Chamber at the Professional Centre, Gzira. The meeting was targeted to all pharmacists practicing in community pharmacies and pharmacy owners participating in the piloting of the POYC together with the pharmacists practicing in community pharmacies and pharmacy owners in the localities served by the Gzira and Rabat health centres. As usual, the pharmacists who are members of the Chamber's Focus Group on the POYC were also invited.

The members of the SAC, supported by members of the Council of the Chamber, gave an update on the pilot project and intensified discussion on patient registration since this was being opened in the remaining

localities of the pilot study and in the first phase of national implementation. The ensuing discussion was enhanced by the proactive participation of those pharmacists who are actively experiencing the POYC and this has contributed positively to the adjustments being made in the continuous process of the project.

Preliminary consideration of the forecasts that had been made during negotiation with regards, for example, to the effect of the POYC on waste of resources, mainly on medicines or on the need to facilitate the pharmacist's interventions to ensure better patient compliance, are being proven to have been correct, albeit officiously, at present. Indeed, several of the pharmacists participating in the pilot and who have started serving their POYC patients have reported that patients are asking not to be given certain medicines to which they are entitled because "they still have some remaining from the last visit".

The main reaction from the public, in particular the elderly and disabled, those who act as carers of their family members and those who, for example, due to work commitments find it difficult to queue at hospital or health centre pharmacies, has been overwhelmingly positive, as expected.

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