NEWSPAPER POST

TheSynapse

The Medical Professionals' Network

MEDICAL IMAGING

# Why are some cancers missed on mammography

by **Pierre Vassallo**
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*Consultant Radiologist*

*Mammography is the standard of reference for the early detection of breast cancer. Screening mammography is performed to detect an abnormality, whereas diagnostic mammography is used to further evaluate the abnormality or a clinical problem.*

The purpose of screening mammography is simply to detect a potential cancer; therefore, the radiologist should not try to make a diagnosis on the basis of screening findings alone. Additional views are important in further assessing an identified abnormality and suggesting appropriate patient treatment. According to data from the Breast Cancer Detection Demonstration Project, the false-negative rate of mammography is approximately 8%–10%. However, it is generally accepted that mammography is able to detect breast cancer in 95% of cases. In other words 5% of breast cancers are missed on initial mammograms. This in itself makes mammography a very accurate test as a true positive rate of 95% is very high. However, one must take into account that there is no medical test that is 100% accurate. Recent studies have emphasized the use of alternative imaging modalities to detect and diagnose breast carcinoma, including ultrasonography (US) and magnetic resonance (MR) imaging. However, high-quality mammography performed with meticulous attention to detail and positioning can significantly enhance the accuracy of image interpretation.

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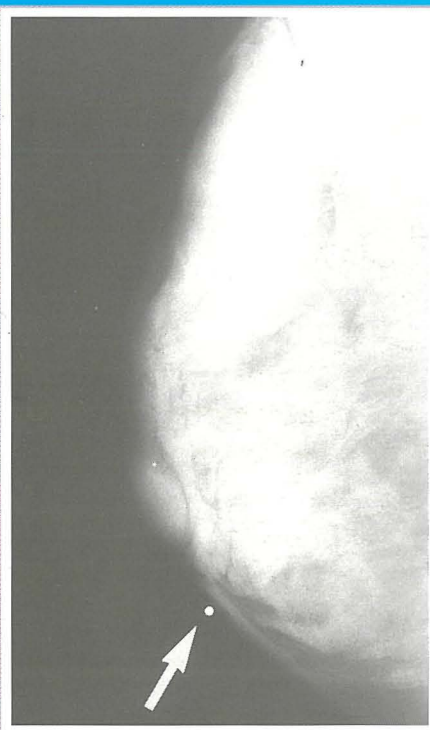

**Figure 1a.** *Invasive ductal carcinoma in a 36-year-old woman with dense breasts and a palpable mass. Left mediolateral oblique mammogram demonstrates no finding that corresponds to a palpable mass (arrow).*

## Editor's Word

Dear Colleagues,

Welcome to the 6th issue of TheSynapse Magazine for 2008. When we consider the number of new services launched during the year we can only feel great satisfaction.

For the past twelve years we have continuously provided medical professionals with news and services relevant to their practice. Our aim has always been to provide a service to our members, that is as comprehensive as possible and therefore we have purposely opted to widen the services to include even those that are not strictly medical as long as it is relevant to medical professionals. As we say … if it's relevant it's on TheSynapse.

We will be concluding the year with the launch of a revamped version of TheSynapse Internet Portal. In this version we will be adding a number of new features including an on-line diary of events and a personal Continuing Medical Education Tracker. There will also be great opportunities for interaction, quizzes and much more. So stay in tune!

Looking forward to an even better 2009.

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***Editor: Dr Wilfred Galea***
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# Why are some cancers m

One of the main limitations on the accuracy of mammography is the dense breast. Breast cancers may be missed because of dense parenchyma that obscures a lesion. Young patients with abundant glandular tissue and low fat content, the latter normally separating and spacing out the breast glands, usually have dense breast. In fact, it is customary to avoid mammography before the age of 35 years for this reason. Small breasts are also usually lacking in fat content and therefore have more closely packed glandular tissue making them dense (Figure 1). Small breasts are also difficult to position on a mammography machine, which influences image quality (Figure 2). Uniformly dense breasts and breasts with areas of increased density within them must be evaluated by ultrasound. This is particularly true if a palpable nodule is present. Palpable nodules

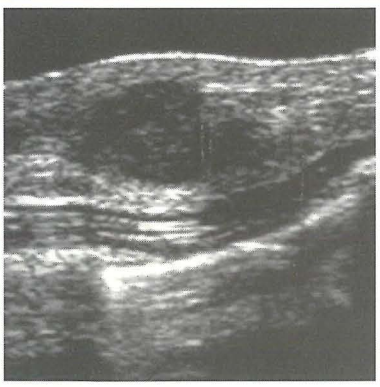

**Figure 1b.** *Invasive ductal carcinoma in a 36-year-old woman with dense breasts and a palpable mass. US image obtained in the area of the palpable abnormality reveals a heterogeneous, hypoechoic mass with irregular margins.*

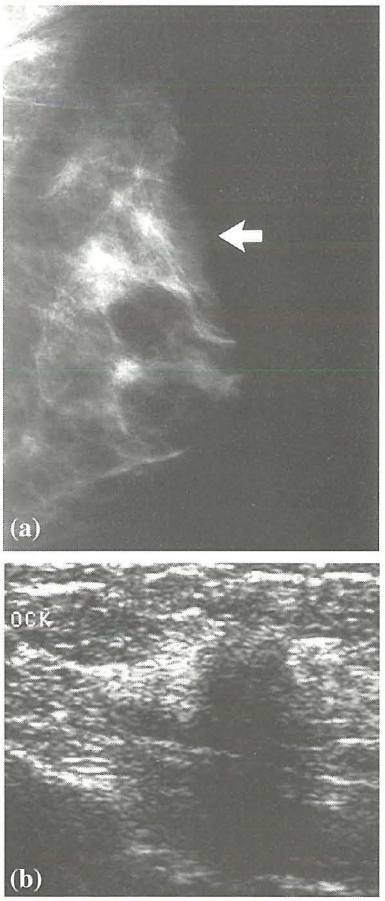


**Figure 2.** *Invasive lobular carcinoma in a 40-year-old woman with dense breasts and no palpable nodule. (a) Right mediolateral oblique screening mammogram shows a small, oval obscured mass superiorly (arrow) that was not seen on the craniocaudal view. (b) US image reveals an incidentally detected irregular mass with acoustic shadowing in the lower outer quadrant.*

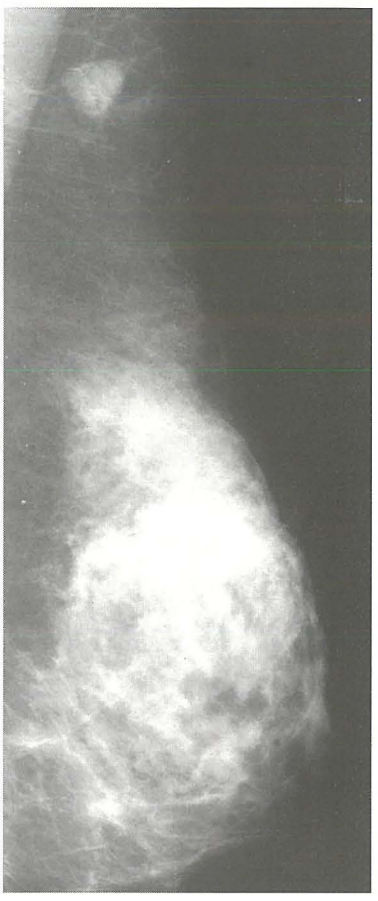

**Figure 3.** *Circumscribed cancer in a 63-year-old woman. Right exaggerated craniocaudal lateral mammogram demonstrates a nonpalpable mass in the axillary tail. The mass is lobulated and circumscribed and has high density. Spot compression mammography would help verify the characteristics of the margins. Pathologic analysis demonstrated mucinous carcinoma.*

# nissed on mammography

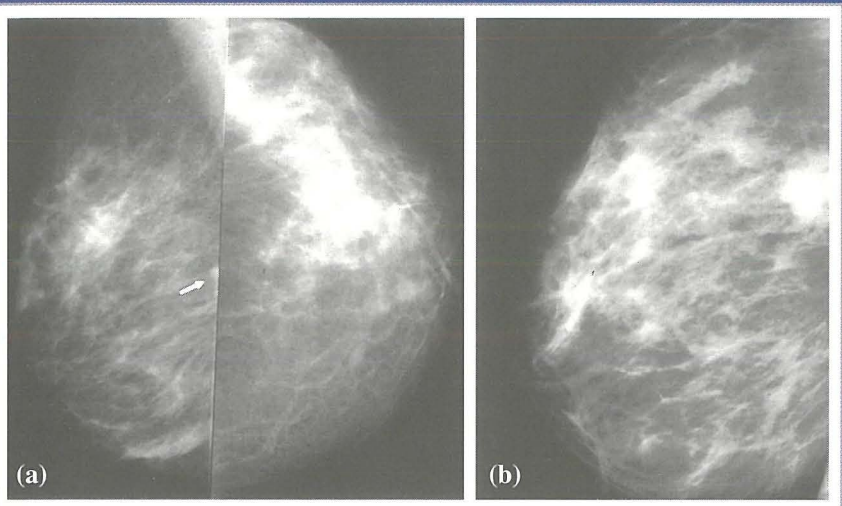


**Figure 4.** *Proper positioning. (a) Left mediolateral oblique (left) and craniocaudal (right) mammograms obtained with improper positioning demonstrate poor visualization of the posterior tissue. The margin of a mass is barely perceptible at the edge of the mediolateral oblique image (arrow). (b) On a left mediolateral oblique mammogram obtained with improved positioning, a cancer is seen near the chest wall. An exaggerated craniocaudal view may also help demonstrate such a mass.*

in dense breasts are often cysts; simple cysts of the breast are easily confirmed by ultrasound and do not require further investigation as they are always benign. However if a palpable nodule is not definitely confirmed to be a cyst on ultrasound, biopsy is required. This holds particularly true for solid nodules with irregular margins and those presenting in women over the age of 30 years of age. In women under the age of 30 years most solid nodules are lobulated and show smooth margins and abundant internal echoes and are most likely fibroadenomas. The latter should be followed by sequential ultrasound exams. Although well-circumscribed cancers are relatively uncommon, they do exist. Medullary, colloid (mucinous), and papillary carcinoma commonly manifest as well-circumscribed masses (Figure 3), so depending on the patient's age and mammographic / ultrasound feature, biopsy should be performed at the least suspicion.

Any solid nodule that has remained unchanged in size and texture over a period of 2 years is assumed to be benign as a cancer would not remain dormant for this period of time. However slow growing cancers are rare but do exist and biopsy should be performed even on stable lesions if these show imaging features of malignancy.

*continues on page 25*

# A practical and comprehensive overview of PET/CT – Part II

## Present day PET/CT: a dual-imaging modality in oncology

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*Clinically, PET/CT has become an integral part of patient management in oncology, neurology and cardiology. By far, oncology accounts for most PET/CT applications.*

### Dual-modality: PET and CT

Many might think that PET and CT were originally incorporated together as we know them today only to help nuclear physicians in accurately localizing the origin of tracer accumulation, hence giving doctors and patients a more definitive report. In actual fact, it was a physicist and an engineer (Townsend and Nutt) who implemented dual-modality in order to overcome one of the major sources of artefacts in PET: attenuation. This is a process by which a beam of radiation is reduced in amplitude and intensity when passing through a material, in this case the radioactive signal emitted from a point source within the body and passing through patient tissues. Attenuation is caused by a combination of absorption and scattering processes. The deeper within the body the source of radiation is, or the denser the tissues, the more the attenuation. To correct for attenuation, transmission (as opposed to emission) images derived from an external positron-emitting source or an external radioactive source, which decays by emission of single events, started being used. This required a blank scan and another transmission scan of the patient. These methods have been used successfully for many years, but were very time-consuming and the radioactive source caused noisy transmission images propagated into PET images. A breakthrough occurred when high resolution, low noise CT transmission maps started being used for attenuation correction. Besides better quality attenuation correction of PET images and significantly shorter scan times, the superimposition of PET and CT improved the interpretation of PET images because anatomic and structural characteristics of tissue were added to the physiologically mediated distribution of the tracer. PET/CT scanners can produce functional PET and anatomical CT data in one session, without moving the patient and with minimal delay between reconstruction and fusion of the two image data sets[1]. Hitting two birds with one stone!

### Applications in oncology

Cancerous cells have high metabolic rates. They use more glucose than normal cells. The most widely available PET/CT radiopharmaceutical today is an analogue of glucose labelled with $^{18}$F, fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) which has a half-life of 110 minutes. It was first used in neuro-oncology by a team led by Di Chiro in the 1980s[2] and then in the detection of lung cancer in the 1990s. $^{18}$F-FDG is injected into the bloodstream, then transported into the interstitial space from where specific glucose transporters carry it into cells. Malignant transformation is associated with increasing energy demands and upregulation of these glucose transporters (especially GLUT-1). Like glucose, $^{18}$F-FDG is phosphorylated by hexokinase to $^{18}$F-FDG-6-phosphate. Unlike glucose though, $^{18}$F-FDG lacks a hydroxyl group on the 2-position and its metabolite $^{18}$F-FDG-6-phosphate cannot act as a substrate for glycolysis. Therefore the positron-emitting tracer is 'trapped' in the cell without being further metabolized, and dephosphorylation is slow. Another advantage of this tracer is that $^{18}$F FDG is eliminated via the kidneys and very little is reabsorbed in the renal tubules, leaving low $^{18}$F-FDG levels in blood.

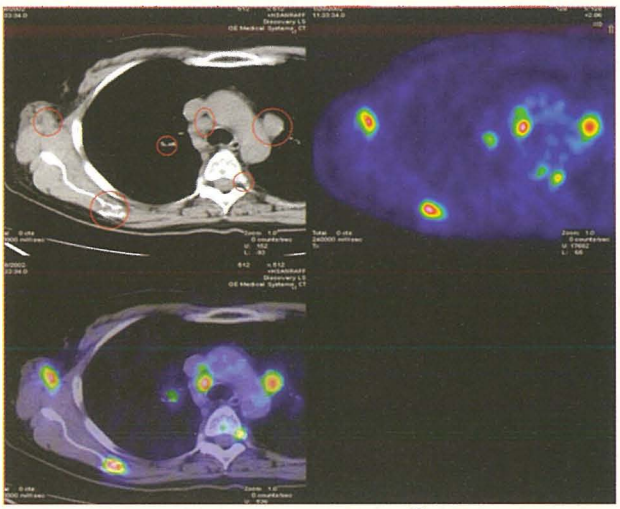

**Figure 1:** *Staging and re-staging using $^{18}$F-FDG. Metabolic PET image superimposed on CT image helps the nuclear physician to report with confidence (Images courtesy of HSR, Milano)*

### Clinical scenarios

$^{18}$F-FDG PET/CT has become an established technique for staging, detection of residual and/or recurrent cancer, significantly for planning therapy, and sometimes for diagnosis. Numerous studies demonstrate how PET/CT is essential in staging and restaging of most cancers including breast, cervical, colorectal, gastric, oesophageal, head and neck, lymphoma, lung, ovarian, uterine, thyroid, testicular, pancreatic, gall bladder and bile duct, renal, bladder, melanoma and sarcoma.

To illustrate further the clinical utility of $^{18}$FDG PET/CT and to highlight the fact that many times this imaging technique is indispensable, some representative and common clinical situations are illustrated below:

**A.** In patients with 'radiologically indeterminate' pulmonary nodules, doctors may opt for a risky 'wait-and-see' or an invasive biopsy which could be marred by complications or false negatives, especially when nodules are in hard-to-reach locations and in cases of inadequate tissue collection. PET/CT has a very high negative predicative value. When negative, a biopsy can be avoided.

*continues on page 6*

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Contra-indications: Hypersensitivity to the active substance or to any of the excipients; renal failure/dysfunction (CrCl <60 ml/min); acute conditions with potential to alter renal function (e.g. dehydration, severe infection, shock, i.v. administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (e.g. cardiac or respiratory failure, recent MI, shock); hepatic impairment, including patients with pre-treatment AST or ALT >3xULN; acute alcohol intoxication, alcoholism; lactation. Precautions: Vildagliptin/metformin tablets should not be used in patients with type 1 diabetes. Lactic acidosis (characterized by acidotic dyspnoea, abdominal pain, hypothermia, coma, decreased blood pH, plasma lactate levels >5mmol/l, increased anion gap and lactate/pyruvate ratio) can occur due to metformin accumulation (e.g. in significant renal failure, hepatic impairment). Other risk factors for lactic acidosis should be assessed (e.g. poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, conditions associated with hypoxia). If metabolic acidosis is suspected, treatment should be discontinued and the patient hospitalised immediately. Serum creatinine should be monitored at least once a year in patients with normal renal function and 2-4 times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients. Special caution should be exercised in elderly patients where renal function may become impaired (e.g. when initiating antihypertensives, diuretics or NSAIDs). It is recommended that LFTs are monitored prior to initiation of Vildagliptin/metformin tablets, at three-monthly intervals in the first year and periodically thereafter. If transaminase levels are increased, patients should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. If AST or ALT persist at 3xULN, vildagliptin/metformin tablets should be stopped. Patients who develop jaundice or other signs of liver dysfunction should discontinue vildagliptin. Following withdrawal of treatment with vildagliptin and LFT normalisation, treatment with vildagliptin should not be reinitiated. In keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended. Vildagliptin/metformin tablets should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards. Vildagliptin/metformin should be discontinued prior to, or at the time of, the administration of iodinated contrast agent and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal. Patients who experience dizziness as a side effect should avoid driving vehicles or using machines. Drug interactions: Vildagliptin has a low potential for interactions with co-administered medicinal products, including drugs that are substrates, inhibitors or inducers of CYP450 enzymes. In pharmacokinetic studies, no interactions were seen with pioglitazone, metformin, glibenclamide, digoxin, warfarin, amlodipine, ramipril, valsartan or simvastatin. As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) are co-administered. Glucocorticoids, beta-2-agonists, diuretics and ACE inhibitors may alter blood glucose. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of Vildagliptin/metformin tablets may need to be adjusted during concomitant therapy and on its discontinuation. Side-effects: The majority of adverse reactions were mild and transient, not requiring treatment discontinuations. General (vildagliptin): rare cases of hepatic dysfunction (including hepatitis). ALT or AST elevations ≥3xULN for vildagliptin 50mg od (0.2%), vildagliptin 50mg bd (0.3%) compared to 0.2% with comparators in clinical trials. Rare cases of angioedema at similar rates to controls. Vildagliptin and metformin in combination common: tremor, headache, dizziness, nausea, hypoglycaemia; uncommon: fatigue. Vildagliptin monotherapy common: dizziness; uncommon: headache, constipation, arthralgia, peripheral oedema, hypoglycaemia; very rare: upper respiratory tract infection, nasopharyngitis. Metformin very common: Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite; common: metallic taste; very rare: LFT abnormalities or hepatitis, skin reactions such as erythema, pruritis and urticaria. Legal Category: POM Packs: 60 tablets; Vildagliptin/metformin (Eucreas®) 50mg/850mg tablets, Vildagliptin/metformin (Eucreas®) 50mg/1000mg tablets (EU/1/07/425/001-018). Marketing Authorisation Holder: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB. Full prescribing information is available on request from Novartis Pharma, P.O. Box 124, Valletta, VLT 1000, Malta. Tel +356 22983217.

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1. Novartis Europharm Ltd. Galvus® Summary of Product Characteristics 2008.
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Eucreas vildagliptin/metformin

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# A practical and comprehensive overview of PET/CT – Part II

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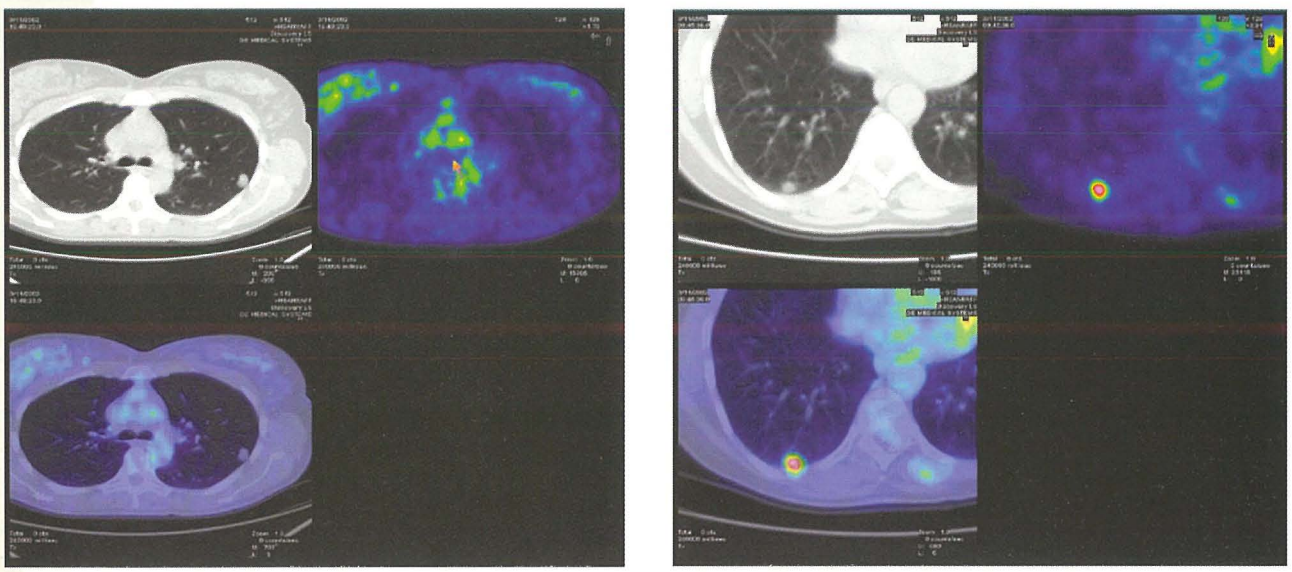

**Figure 2:** *Two patients presenting with a pulmonary nodule. In one patient (above left), the nodule showed no tracer uptake, and a biopsy was avoided. In the other patient (above right), the nodule showed avid tracer uptake. Moreover, whole-body PET/CT allowed immediate staging of the patient with the very suspicious lung lesion. Metabolic characterisation of pulmonary nodules is also very important when these are located in areas which are impossible to reach by a biopsy needle (Images courtesy of HSR, Milan)*

**B.** PET/CT is more sensitive than CT in pre-operative staging of most carcinomas; for example, many studies show that in oesophageal carcinomas, a significant number of patients deemed operable by CT may have unsuspected metastases which can be identified by PET/CT, hence drastically altering management[3].

**C.** A drawback of 'conventional' imaging techniques is their reliance on size criteria to define disease such as in the case of lymph nodes, with the consequent failure to detect disease in small lymph nodes and to exclude disease in larger lymph nodes. $^{18}$F-FDG often permits distinction of suspicious lymph nodes as malignant or disease-free, also avoiding unnecessary procedures such as biopsies or mediastinoscopies. PET/CT staging and restaging (assessment of therapy) of Hodgkin's and non-Hodgkin's lymphoma is superior to stand alone CT and gallium scintigraphy[4].

**D.** In some carcinomas it is possible to follow-up using tumour markers (e.g. colorectal, ovarian, breast and pancreatic carcinomas). PET/CT is an asset in patients presenting with rising tumour markers during follow-up and with negative conventional morphological imaging. PET/CT allows the addition of early metabolic change data to the morphological images, potentially determining the cause of tumour marker rise. FDG-PET is also a valuable diagnostic tool in patients with cancer of unknown primary (which conventional imaging modalities fail to detect). These patients would initially present with metastasic lesions (e.g. bone, lymph nodes, lung)[5].

**E.** Increased tumour uptake is a function of proliferative activity and is also related to viable tumour cell number. Hence, if $^{18}$F-FDG is related to tumour cell viability, then reduction in uptake (with effective chemotherapy) should reflect increased tumour cell killing rate. Clinical trials have demonstrated uptake of $^{18}$F-FDG as an early and sensitive pharmacodynamic marker of the anti-tumoral effect of chemotherapy, even as early as the first cycle of chemotherapy[6]. The oncologist can consider changing a chemotherapy regime early on, avoiding extra costs in suboptimal therapies and saving the patient from side-effects.

**F.** When a patient presents with a tumour (as in lung carcinoma) with surrounding oedema, PET/CT permits the evaluation of the exact extent of the lesion, thus allowing better radiotherapy planning. Nowadays, PET images are used directly for radiotherapy purposes. Post-radiotherapy PET/CT helps determine whether any residual viable tumour is still present. This is difficult to distinguish on CT because both scar tissue (radiotherapy changes) and disease can alter anatomy.

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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, VLT 1000, Malta. Tel +356 22983217. (vsn 2008-MT-Oct)

# The commonly held image of women with osteoporosis as fragile and hunched over is outdated

*Known as the silent epidemic, osteoporosis is a global health concern affecting 200 million men and women worldwide.*

Timeless Women
The Campaign for Stronger Bones

1 out of 3 women over the age of 50 will sustain a fracture because of osteoporosis.
1 out of 5 men and women over 50 who have suffered a hip fracture will die within a year.
Loss of function and independence among post-fractured patients is profound, with 40% unable to walk independently and 60% requiring assistance a year later.

These are shocking statistics.

Undoubtedly, osteoporosis is a serious problem which carries great morbidity and loss of function.

But do medical practitioners really understand the full impact of this condition? Do women with osteoporosis and their doctors have the same perceptions of the impact of osteoporosis on a woman's daily life? The Timeless Women survey was carried out to understand better the lifestyles and attitudes of women with osteoporosis and compare those with the beliefs of doctors who see and treat women with the disease. It was designed to find out who today's woman with osteoporosis really is, and in particular whether their treatment fits into their lifestyle or is convenient for them. The research was undertaken among doctors who care for women with osteoporosis and women who are affected by the disease. The Timeless Women report was launched on World Osteoporosis Day, on 13th October 2008.

Doctors surveyed saw at least 14 women with osteoporosis a month, with the average seeing 65 women with osteoporosis per month. The average age of doctors was 51 years. The women who were surveyed were between 55 and 64 years, had been diagnosed with osteoporosis and were either currently taking medication for their osteoporosis or had taken medication in the last two years. The women interviewed were not patients of the doctors interviewed and all interviews were conducted anonymously by telephone. Data was weighted using 'Rim weighting' to ensure the number of women surveyed was reflective of the total number of women with osteoporosis in each country. In a similar way, the data for doctors reflected the total number of doctors practicing in each country surveyed. No quota was placed on the age or gender of the respondents. All interviews were conducted in the respondents' native language. 100 doctors and 200 women with osteoporosis were interviewed in France, Germany, Mexico, Switzerland and the UK, with a total survey population of 1,500.

| What doctors surveyed think and feel: | What women surveyed with osteoporosis think and feel: |
|---|---|
| 69% do not perceive women with osteoporosis to be very active. A significant proportion of doctors perceive female osteoporosis patients to be less likely to engage in a range of activities than non-osteoporosis patients of the same age.<br>75% believe that osteoporosis has a negative impact on their patients' outlook on life | Only 23% describe themselves as 'frail and fragile'. More than 1 out of 5 women deem that their doctor thinks of them as being more frail and dependant than they really are. Less than 33% believe that the disease has a negative impact on their outlook on life |

The picture that unfolds throughout the report is one of a mismatch between the opinions and attitudes of women with osteoporosis and the doctors who treat the disease.

Most medical professionals still perceive the typical person who has osteoporosis as a fragile and hunched over woman. Yet many women with osteoporosis consider themselves to be in the prime of their life, active, busy and full of life. These women work, travel and do not want osteoporosis to slow them down.

Doctors' perception is an important barrier in the diagnosis and management of osteoporosis and it is essential that medical professionals consider the possibility of osteoporosis in a wider spectrum of the population. Many women (and men) with osteoporosis remain undiagnosed simply because they do not undergo diagnostic tests until they sustain an osteoporotic fracture – at which point the morbidity shoots up.

The golden standard for assessment of Bone Mineral Density is the DEXA scan, however if a doctor has no access to DEXA facilities, the FRAX® tool is increasingly being used to calculate the ten-year probability of fracture of an individual. The FRAX® tool has been launched by WHO and is a major milestone towards helping physicians to improve identification of patients at high risk of fracture for treatment. It is an algorithm, combining risk factors such as age, sex, weight and smoking habits, and femoral neck bone mineral density if available. This practical web-based tool gives a figure indicating a ten-year fracture probability as a percentage, which provides guidance for determining the need of treatment (www.shef.ac.uk/FRAX/).

Persons diagnosed with osteoporosis are advised on general lifestyle measures including a diet that ensures adequate intake of Calcium and Vitamin D. Advice regarding exercise is most important. However, many cases warrant the prescription of anti-osteoporosis medication. There could be a number of barriers to medical treatment – not last being the price of medication which in Malta can cost anywhere between Eur 450 and Eur 600 per year.

*continues on page 25*

# INTRODUCING ACLASTA®

## THE ONCE-YEARLY INFUSION OF POWERFUL

# OSTEOPROTECTION

**NEW FOR POSTMENOPAUSAL OSTEOPOROSIS**

- Significantly reduced 3-year risk of fractures at all key osteoporotic sites[1]*

| 70% | 41% | 25% |
|---|---|---|
| risk reduction in vertebral fracture[1] | risk reduction in hip fracture[1] | risk reduction in nonvertebral fracture[1]** |

- A 15 minute, once-yearly infusion ensures yearlong compliance[1]
- Most adverse events were transient and mild to moderate[1,2]
- Patient-preferred over weekly oral alendronate[3,4]

*Relative to placebo.[1]

**Nonvertebral fracture includes wrist, rib, arm, shoulder, or hip fracture; excludes finger, toe, or craniofacial fracture.[1]

**Aclasta® 5 mg**

**PRESENTATION:** Zoledronic acid. 100 mL solution bottle contains 5 mg zoledronic acid (anhydrous), corresponding to 5.330 mg zoledronic acid monohydrate.

**INDICATIONS:** Treatment of osteoporosis in post-menopausal women and men at increased risk of fracture, including those with a recent low-trauma hip fracture. Treatment of Paget's disease of the bone.

**DOSAGE AND ADMINISTRATION:** Osteoporosis: A single intravenous infusion of 5 mg Aclasta administered once a year. In patients with a recent low-trauma hip fracture, it is recommended to give the Aclasta infusion two or more weeks after hip fracture repair. Paget's Disease: A single intravenous infusion of 5 mg Aclasta. Specific re-treatment data are not available for Paget's disease. Aclasta is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes. Patients must be appropriately hydrated prior to administration of Aclasta, especially important for the elderly and for patients receiving diuretic therapy. Adequate calcium and vitamin D are recommended in association with Aclasta administration. In patients with recent low-trauma hip fracture a loading dose of 50,000 to 125,000 IU of Vitamin D is recommended prior to the first Aclasta infusion. Not recommended for use in patients with severe renal impairment (creatinine clearance <35 ml/min). No dose adjustment in patients with creatinine clearance ≥35 mL/min, or in patients with hepatic impairment, or in elderly patients. Aclasta should not be given to children or adolescents.

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

**PRECAUTIONS AND WARNINGS:** Serum creatinine should be measured before giving Aclasta. Not recommended in patients with creatinine clearance <35 ml/min. Appropriate hydration prior to treatment, especially in the elderly and in combination with diuretics Use with caution in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration), Pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly advised that patients with Paget's disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget's disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. A patient being treated with Zometa should not be treated with Aclasta. As a precaution against osteonecrosis of the jaw (ONJ) a dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

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

**ADVERSE REACTIONS:** The incidence of post-dose symptoms (e.g. fever, myalgia, flu-like symptoms, arthralgia and headache) are greatest with the first infusion and decrease markedly with subsequent infusions. The majority of these symptoms occur within the first three days and were mild to moderate and resolved within three days of the event onset. The incidence of post-dose symptoms can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration. Very common: Fever Common: Flu-like symptoms, chills, fatigue, pain, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, pain in extremity, vomiting, nausea, headache, dizziness, atrial fibrillation, hypocalcaemia†, rigors† . Local reactions: redness, swelling and/or pain Others: renal dysfunction and osteonecrosis of the jaw. † Common in Paget's disease only.

**PACK SIZE:** Aclasta is supplied in packs containing one 100ml bottle

**LEGAL CATEGORY:** POM.

**MARKETING AUTHORISATION NUMBER:** EU/1/05/308/001.

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

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

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

NOVARTIS

Aclasta®
zoledronic acid 5 mg
solution for infusion
*One Infusion. Yearlong Osteoprotection.*

ACL Ad1 1-'08 MT

# The New 24/4 Oral Contraceptive Pill

*by* **Yves Muscat Baron** *MD PhD FRCOG FRCPI*
*Consultant Obstetrician and Gynaecologist*
*Mater Dei Hospital*

*"It is our experience, as it was our aim, that as a result of child-spacing, and adequate care of mothers, death rates would be reduced. It is now a fact that as a result of birth control, the survival rate among mothers and children is higher. There is less suffering for all groups"*

***Margaret Sanger, 1947***

## Historical Background

The above quotation came from Margaret Sanger, then President of the American Society of Family Planning, who had the vision that family planning would holistically be beneficial to society. In fact in 1951, Margaret Sanger through her ardent supporter, Katherine Dexter Mc Cormick, collected a total of $150,000 (a substantial amount for the time) so as to fund research on oral contraception. With this funding Dr Gregory Pincus commenced preclinical trials suppressing ovulation in rabbits. Within a decade Dr Carl Djerassi was able to produce the first oral contraceptive pill which was initially tested in Puerto Rico and Haiti.

Since the 1950's, gynaecological endocrine research in the form of the combination of a progestogen and an oestrogen, given either for postmenopausal hormone replacement or for contraception, remains the most scientifically studied medical treatment. Moreover these gynaecological endocrine developments have probably been the most socially beneficial medical therapy of all time. Despite over half a century of scientific development, improvements in contraceptive regimens are still being developed.

## Introduction

The most recent development is the use of a new progestogen drospirenone, whose antimineralocorticoid and antiandrogenic properties lead to improvements in both physical and psychological well-being. Better progestogens with a longer half-life allow a reduction or even an obliteration of the pill free interval and hence a lessening of menstrual-related side effects.

Progesterone has a high affinity for the mineralocorticoid receptor and is an antagonist of aldosterone. Almost all synthetic progestogens are devoid of an antimineralocorticoid effect, and are unable to antagonize the salt-retaining effect of oestrogens. The results of clinical studies with drospirenone, demonstrate significant antialdosterone activity.

Another new development is the 24/4 extended pill formulation. This entails the reduction in the pill free period from seven to four days. The pill free period was suggested in the early pill regimens in an effort to mirror the body's physiological hormonal patterns. It may also have been introduced to assuage the prescriber's 'clinical conscience' and to allay his patient's fears that the body would be given a 'rest' from the unnatural hormonal ingestion.

Extended pill formulations have several advantages. It is postulated that in practice an extended pill regimen should compensate for inadvertent pill omission reducing the risk of failed contraception. Premenstrual somatic and psychological symptoms are at their highest during the pill free period. Shortening this pill free period together with a long half-life progestin should be able to reduce these undesirable effects.

## Scientific Evidence on the New 24/4 OCP

One of the main causes for failure of oral contraception is lack of compliance. Over fifty percent of women taking the oral contraception discontinue or inadvertently omit its ingestion within the first year of its prescription. Recent studies indicate high user satisfaction with drospirenone 3mg and with both ethinyloestradiol formulations of 30µg and 20µg. In the pivotal trial of Bachmann et al, 86% of women were 'satisfied' or 'very satisfied' with this treatment. Significant proportions, 37.9% and 29.3% of women, reported that physical and emotional well-being, respectively, improved during treatment versus baseline. Moreover, 72.7% of women would have continued with the study medication if given the choice.

Epidemiological reviews regarding menstruation have shown that the majority of women prefer monthly withdrawal bleeds. Again in the pivotal efficacy study, 24/4 drospirenone 3mg and ethinyloestradiol 20µg formulation, had a positive effect on menstruation in the great majority of women. At baseline, 89.6% had satisfactory withdrawal bleeds and this increased to 94.4% through to cycle 13. The severity of withdrawal bleeding was described as 'spotting' to 'normal' in ≥88% of women. Bleeding patterns as assessed in a 7-cycle open-label randomized study, in the 24/4 drospirenone 3mg and ethinyloestradiol 20µg regimen [n=229] were lighter than the desogestrel 150µg and ethinyloestradiol 20µg regimen [n=220]. The majority of women (>80% during cycles 2 to 13) experienced no intermenstrual bleeding.[1] This impact on menstrual flow may be ideal for women suffering from menorrhagia.

| Symptoms | Hormone treatment (21 days) % | Hormone-Free Interval (7 days) % | P-value |
|---|---|---|---|
| Pelvic pain | 21 | 70 | <0.001 |
| Headaches | 53 | 70 | <0.001 |
| Breast tenderness | 19 | 58 | <0.001 |
| Bloating/swelling | 16 | 38 | <0.001 |
| Use of pain medications | 43 | 69 | <0 001 |

**Table 1:** *Menstruation-related symptoms and 21/7 oral contraception*

The above table regarding oral 21/7 contraception and menstrual symptoms, clearly shows the significant increase in somatic symptoms during the 7 day hormone free period. It was postulated that reducing the duration of the hormone-free period from 7 to 4 days may influence the above symptoms which are frequently a cause for pill discontinuation.

The physiological rationale for shortening the hormone-free interval resulted in avoiding hormonal fluctuations. It is critical that follicular development is efficiently suppressed so as to avoid endogenous oestradiol production. FSH increases during the pill-free interval leading to follicular growth and oestradiol production. Oestradiol fluctuations have been correlated with oral contraception related side-effects. Moreover many of these symptoms are related to increased water retention.

*continues on page 12*


YAZ®

Freedom like never before

**YAZ® Prescribing Information**

**YAZ® 0.02 mg / 3 mg film coated tablets. Indication:** Oral contraception. **Composition:** 24 light pink film-coated tablets containing 0.020 mg ethinylestradiol (as betadex clathrate) and 3 mg drospirenone. 4 white placebo (inactive) film-coated tablets containing no active substances. **Posology:** The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2-3 after starting the placebo tablets (last row) and may not have finished before the next pack is started. **Contraindications:** Venous or arterial thrombosis in prodromal conditions, present or in history or risk factors for it. Cerebrovascular accident in prodromal conditions, present or in history or risk factors for it. Hereditary or acquired predisposition for venous or arterial thrombosis. Pancreatitis present or in history. Presence or history of severe hepatic disease. Severe renal insufficiency or acute renal failure. Presence or history of liver tumours. Known or suspected sex-steroid influenced malignancies. Undiagnosed vaginal bleeding. History of migraine with focal neurological symptoms. Hypersensitivity to the active substances or to any of the excipients of YAZ film-coated tablets. **Warnings and Precautions:** Circulatory disorders or risk factors for it. Tumours. Other conditions: moderate renal impairment and concomitant use of potassium-sparing medicinal products. Present or history of hypertriglyceridemia, hypertension. Occurrence or deterioration with both pregnancy and COC: jaundice and/or pruritus related to cholestasis, gallstones, porphyria, systemic lupus erythematosus, haemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss. In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema. Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use. Chloasma. Galactose intolerance. Prior to the initiation of YAZ a complete medical history should be taken and pregnancy must be ruled out. The efficacy of COCs may be reduced in the event of e.g. missed active tablets, gastro-intestinal disturbances during active tablet taking. With all COCs, irregular bleeding may occur, especially during the first months. In some women withdrawal bleeding may not occur during the placebo tablet phase. If the COC has been taken according to the directions it is unlikely that the woman is pregnant. **Undesirable effects:** Common side effects reported in clinical trials include emotional lability, headache, nausea, breast pain, metrorrhagia, and amenorrhea. For uncommon and rare side effects and details see full SPC. The following serious adverse events have been reported in women using COCs: Venous/ arterial thromboembolic disorders, hypertension, liver tumours, occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, endometriosis, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice, chloasma. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema. The frequency of diagnosis of breast cancer is very slightly increased among OC users. **On prescription only.** Date of Revision of the Text: July 2008. **Please note!** For current prescribing information refer to the full SPC and /or contact Alfred Gera and Sons Ltd. on + 356 21 446205. **Bayer Schering Pharma AG, European Business Unit Women's Healthcare, 13342 Berlin, Germany, www.bayerscheringpharma.de**

Bayer HealthCare
Bayer Schering Pharma

# The New 24/4 Oral Contraceptive Pill

*continued from page 10*

The 24/4 drospirenone 3 mg and ethinyloestradiol 20µg formulation has been shown to maintain the same concentrations in total body water and extracellular water as observed in the follicular phase. This effect is likely due to the antimineralocorticoid activity of drospirenone, which counteracts the water retention elicited by oestrogen.[2] The 30 hour half-life of drospirenone extends its antimineralocorticoid into the shortened 'hormone free period' reducing the incidence of menstrual related somatic side-effects. In fact, the 24/4 drospirenone 3mg and ethinyloestradiol 20µg formulation led to significant reductions in breast tenderness, bloating, weight gain and headache by $p < 0.0033$ and $p < 0.0001$ in the cross-over study and parallel studies respectively.

The effect on lipid and carbohydrate metabolism and haemostatic factors over 7 cycles of 24/4 3mg drospirenone and 20µg ethinyloestradiol formulation were also assessed. These effects were compared to desogestrel 150µg / ethinyloestradiol 20µg indicating that both treatments increased the beneficial HDL-cholesterol and decreased the deleterious LDL-cholesterol. Haemostatic factors and blood glucose levels measured through glucose tolerance tests remained within normal limits.

Oral contraceptives have long been a useful adjunct in the armamentarium against acne. Two placebo-controlled studies utilizing the 24/4 drospirenone 3 mg and 20µg ethinyloestradiol formulation were conducted in a total of 1072 women complaining of moderate acne over 6 cycles. Both studies resulted in significantly ($p<0.0001$) greater reductions in mean change from baseline in inflammatory, non-inflammatory and total acne lesion counts versus placebo. These results are likely to have been mediated through the anti-androgenic effects of drospirenone.

Oral contraceptive-induced hypertension occurs in approximately 5% of OCP users. This a well-recognized phenomenon characterized by an increase in blood pressure levels after beginning oestrogen/progestin therapy and a reduction to normal levels within 1 year after suspension of the therapy. The pathophysiology of this condition is still not understood although several lines of evidence indicate a role for a genetic susceptibility to the development of this condition. In postmenopausal women receiving hormone replacement in the form of drospirenone /17-beta oestradiol, blood pressure was reduced by -8.6/-5.8 mm Hg versus -3.7/-2.9 mm Hg in those receiving placebo ($P < 0.01$ for both SBP and DBP). In the pivotal efficacy study, blood pressure levels in women taking oral contraception utilizing 24/4 drospirenone 3 mg and 20µg ethinyloestradiol formulation remained within normal limits. The drospirenone component may be protective against oral contraceptive-induced hypertension.

As the efforts of Pincus and Djerassi testified more than 50 years ago, the raison d'etre of the oral contraceptive pill is ovulation suppression with resultant contraception. Out of a total of 2004 woman years of exposure to 24/4 drospirenone / ethinyloestradiol regimen across 4 phase III efficacy and cycle control studies a total of 16 pregnancies were observed. This resulted in a Pearl Index of 0.8 for typical use and calculated to be 0.41 for perfect use. This corresponds to more than 99% contraceptive protection.

The first pill in any oral contraceptive pack is the most important pill in preventing pregnancy. Omission of the first pill increases the likelihood of escape ovulations. Suppression of follicular development as determined by the Hoogland scores (transvaginal ultrasound scoring for follicular assessment) was more pronounced with 24/4 compared to 21/7, drospirenone /ethinyloestradiol formulations (table 2). In the case of three missed pills, a lower incidence of escape ovulations occurred with the 24/4 regimen compared to the 21/7 regimen (2% versus 8%, respectively). The 24/4 regimen consistently suppressed endogenous estrodiol and consequent FSH and LH levels more than the 21/7 regimen.

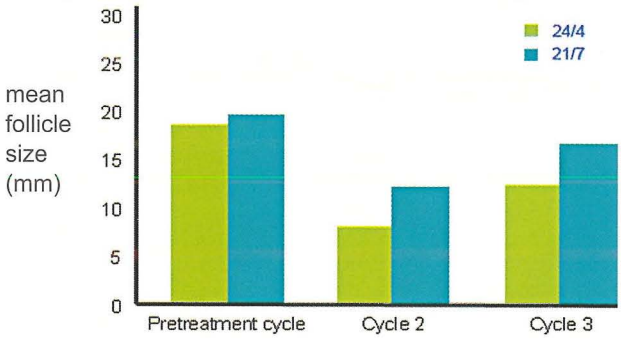


**Table 2:** *Ovulation inhibition study*

## Conclusion

What would the world be without hormonal contraception? Undoubtedly millions of unplanned pregnancies would have occurred and as a consequence the spectre of abortion, already rife especially in Eastern Europe and the former Soviet Union, would reach catastrophic proportions globally. Noncontraceptive advantages as avidly demonstrated by the 24/4 drospirenone / ethinyloestradiol formulation certainly alleviate the burden on the health services to treat menorrhagia, irregular menstrual bleeding, acne, and the premenstrual syndrome. Epidemiological studies ascertain that without the pill there would be many more deaths from ovarian and endometrial cancer, and from complications following hysterectomy or anaemia. Margaret Sanger's vision that family planning would impact our social welfare was indeed very close to the truth – ***"the survival rate among mothers and children is higher. There is less suffering for all groups"***.

### References

**1.** Bachmann G, Sulak PJ , Sampson-Landers C et al. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20Ïg ethinylestradiol and 3mg drospirenone. *Contraception* 2004; 70(3):191–8.

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Pearlstein T, Bachmann G, Zacur H, Yonkers K. Treatment of premenstrual dysphoric disorder with a new drospirenone – containing oral contraceptive formulation. *Contraception* 2005; 72(6):414-21.

# THE BIG DROP

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- Powerful BP Reduction across all grades of hypertension [1, 2]
- Up to -43mmHg SBP reductions [2]
- 9 out of 10 patients achieve BP goal [1]
- Less peripheral oedema compared with amlodipine monotherapy [2]


References:
1. Philipp T. et al, Clin Therapeutics 2007; 29 (4); 563-80
2. Poldermans D. et al. Clin Therapeutics 2007; 29(2); 279-289


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**GREAT DROPS JUST GOT BETTER[1]**

**Exforge® Film-coated tablets**
**Presentation:** Amlodipine and valsartan 5 mg/160 mg, 10 mg/160 mg film-coated tablets. **Indications/Posology:** Treatment of essential hypertension in patients whose blood pressure is not adequately controlled on amlodipine or valsartan montherapy. Recommended dose is one film-coated tablet per day (5 mg amlodipine and 160 mg valsartan, or 10 mg amlodipine and 160 mg valsartan). **Contraindications:** Hypersensitivity to any component of Exforge or to dihydropyridine derivatives. 2nd and 3rd trimesters of pregnancy. Severe hepatic impairment, biliary cirrhosis or cholestasis. Severe renal impairment (GFR <30ml/min/1.73 m2) and patients undergoing dialysis. **Precautions/Warnings:** Risk of hypotension in sodium- and/or volume-depleted patients. Beta-blocker withdrawal should be gradual. No data available in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney or after recent kidney transplantation. Monitoring of potassium levels and creatinine in moderate renal impairment. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan. As with all other vasodilators, special caution in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. Exforge has not been studied in any patient population other than hypertension. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur. Avoid use in women planning to become pregnant and while breast-feeding. Not recommended during the first trimester of pregnancy. Not recommended in patients below 18 years of age. Caution when using potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium or any other medicinal product that may increase potassium levels. Primary hyperaldosteronism. In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. **Interactions:** Caution is required with concomitant use of CYP 3A4 inhibitors (eg. ketoconazole, itraconazole, ritonavir), CYP 3A4 inducers (eg carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, hypericum perforatum). Caution is required when used together with NSAIDs, COX-2 inhibitors, acetylsalicylic acid and non-selective NSAIDs. Conomitiant use is not recommended however if the combination proves necessary, caution and monitoring of serum potassium levels when used concomitantly with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium level and of serum lithium levels when used with lithium. **Adverse reactions: The most common adverse reactions are:** Nasopharyngitis, influenza, headache, oedema peripheral, pitting oedema, facial oedema, fatigue, flushing, asthenia, vertigo, tachycardia, palpitations, orthostatic hypotension, cough, pharyngolaryngeal pain, diarrhoea, nausea, abdominal pain, constipation, rash, erythema, joint swelling, back pain, arthralgia, dizziness, somnolence, dizziness postural, paraesthesia. Peripheral oedema, a recognised side-effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. **Rare adverse reactions but potentially serious are:** Hypersensitivity. **Additional potentially serious adverse experiences reported in clinical trials with amlodipine monotherapy are:** Gastritis, gingival hyperplasia, gynaecomastia, leucopenia, myalgia, pancreatitis, hepatitis, thrombocytopenia, vasculitis. **Additional potentially serious adverse experiences reported in clinical trials with valsartan monotherapy are:** Viral infections, upper respiratory infections, sinusitis, rhinitis, neutropenia, insomnia. Altered renal function, especially in patients treated with diuretics or in patients with renal impairment, angioedema and hypersensitivity (vasculitis, serum sickness) can occur. Please refer to SmPC for a full list of adverse events. **PACK SIZE:** 14, 28 film-coated tablets. **LEGAL CATEGORY:** POM. **MARKETING AUTHORISATION NUMBER:** EU/1/06/370/002 – 3/ EU/1/06/370/10-11. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. Consult full Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma, P.O. Box 124, Valletta VLT 1000, Malta. Tel +356 22983217 (vsn 2008-MT).

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EXF Ad1 11/08 MT

MAP

THE SOCIETY OF ORTHOPAEDIC MEDICINE

# POST GRADUATE DIPLOMA IN ORTHOPAEDIC MEDICINE IN MALTA THROUGH THE SOCIETY OF ORTHOPAEDIC MEDICINE

## WHAT IS THE COURSE ABOUT?

This exciting programme is designed for physiotherapists and medical doctors to develop and refine clinical reasoning and practical skills. The successful completion of the programme denotes eligibility to join the Society of Orthopaedic Medicine as a full member. The diploma should take approximately 12-18 months to complete and is a combination of taught modules, interactive group work and self directed study with continuous assessment throughout. The programme is split into three modules:

- **Module A** (4 days): Cervical Spine and Upper Limb
- **Module B** (4 days): Lumbar Spine and Lower Limb
- **Module C** (5 days): Revision of A and B; Thoracic Spine and Sacroiliac Joint; Advanced Techniques for Cervical and Lumbar Spine; Principles of Lumbar Injections; SOM Membership Examination

Each module is very practical and there is an emphasis on students actively participating. A gap of four months should be left between modules to enable practice and assimilation of techniques. On conclusion of the three modules, students have the opportunity to submit a reflective essay for the award of the SOM Diploma in Orthopaedic Medicine.

## WHAT WILL I ACHIEVE?

By the end of the course you will have:

- Developed your ability to apply functional anatomy
- Established an accurate diagnostic approach
- Developed mastery in manual techniques:
  - clinical examination
  - transverse friction massage
  - graded mobilisations
  - manipulation
- An understanding of the application of injection techniques
- Extended your clinical reasoning skills
- Eligibility to become a full member of SOM (subject to passing the examinations)
- Eligibility to attend the SOM Diploma in Injection Therapy, and the Diploma in Advanced Clinical Practice (subject to achieving full SOM membership)

**The Malta Association of Physiotherapists have successfully brought this prestigious course to Malta on the following dates:**

| | | | | |
|---|---|---|---|---|
| **Module A** | **20 February** | - | **23 February 2009** | **€ 520** |
| **Module B** | **26 June** | - | **29 June 2009** | **€ 520** |
| **Module C** | **14 January** | - | **18 January 2010** | **€ 675 (including examination fee)** |

**Venue:** **Mater Dei Hospital, Physiotherapy Department**

For further information on the Malta SOM PG Diploma in Orthopaedic Medicine modules please contact:
Josef Pace via e-mail pacejosef@gmail.com / 9982 2271 or

Madeleine Ottewell via email admin@somed.org / telephone 0044 845 680 1678.

Visit www.physiomalta.com / www.somed.org

Booking is done online via the Society of Orthopaedic Medicine **www.somed.org/somdip/index.asp#apply**

# Winners of the YAZ® e-Quiz

The month of October saw the launch of the new 24/4 oral contraceptive – YAZ® – in Malta. As part of the launch, members of TheSynapse were invited to participate in the YAZ® e-Quiz which consisted of 10 True/False questions based on a review article titled 'Shortening the hormone-free interval' by Mishell et al. and prepared courtesy of the local Bayer Schering Pharma Team.

The article focuses on the medical benefits of a shortened pill-free interval and the positive impact this has on ovarian suppression and on cyclical hormonal fluctuations and, therefore, on the physical and emotional well-being of the individual.

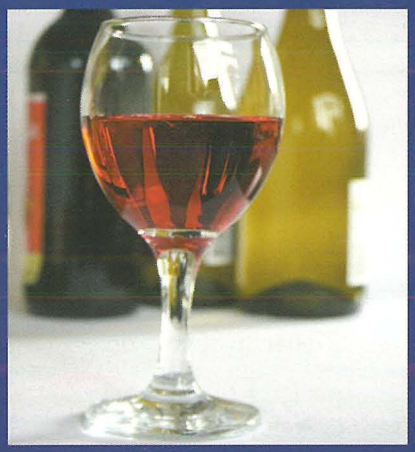
We would like to congratulate Drs Dominic Agius and Astrid Muscat Baron as the prize winners for the YAZ® e-Quiz 2008 and Well Done to all the participants.

The Bayer Schering Team

# 'GRAPE EXPECTATIONS' – An Introduction to Wine Enjoyment

Albert Cilia-Vincenti

Wine is totally different from other alcoholic drinks – its taste characteristics depend on a whole array of complex factors, including grape variety, grape maturation, type of minerals in the soil, pattern of rainfall and soil drainage, vineyard altitude and sun direction, vinification in oak barrels or not, etc., etc. The taste characteristics of wine made from the same grape variety therefore may vary enormously unlike, say, two different bottles of gin.



This introduction to enjoying wine will start from first principles. I feel this is necessary because some of these basic requirements of wine tasting are omitted, in part or whole, even by some wine aficionados. The intention is not to offend anybody's intelligence, but simply to lay down some basic rules, as with any skill apprenticeship.

Drinking and tasting are two different functions altogether. When you drink water, a soft drink, a beer or a gin & tonic, you tend to swallow the liquid straight way, and it passes immediately from lips to throat to stomach in a split second, thereby getting some quick pleasant sensation in the mouth and throat. Furthermore, if you're concentrating on something else, as you're drinking this liquid, you notice even less its characteristics as it shoots down the gullet.

The first basic requirement for wine appreciation is therefore to make sure you know how to sip wine in small quantities and how to make it go all round your tongue and mouth before swallowing. When you then eventually swallow, you note what sensations the wine leaves in your throat and for how long these sensations last after you've swallowed – great wines leave pleasant and complex aromas in your throat and nasal cavities lasting many seconds – one of the crucial criteria for wine quality assessment, which is so often overlooked by the less knowledgeable.

It follows that mental concentration on the aromas and flavours in your mouth and throat is another fundamental requirement. This is not easy at table with other diners, where you would be listening and contributing to conversation, but it is a mental discipline needing cultivation. When you are mindful of what sensations food and wine are leaving in your mouth, you are able to eat smaller food portions and drink less wine than when you're gulping down whole platefuls and glassfuls without thinking about it whilst arguing about some hot political or work-related topic. This discipline of thoughtful food and wine tasting, besides being fundamental in culinary enjoyment, is also one of the important components of an obesity-combating strategy.

The third basic requirement is learning to concentrate on the aroma of the wine. Although I've left smelling wine till the end of this introductory piece, assessing a wine's bouquet (its 'nose') is of utmost importance, because none of the other senses are so powerful and pleasurable as our sense of smell. Furthermore, the sense of taste is so dependent on the sense of smell, that when the latter is impaired, you do not taste properly, or not at all. A recently discovered large family of genes, in nasal cavity epithelium, controls protein olfactory receptors which recognise thousands of incoming odorant molecules. They transmit this information to the brain's limbic system which analyses it by scanning its vast memory bank for related matches. The limbic system is involved in emotion, motivation and emotional association, and has a role in formation of memory by integrating emotional states with stored memories of physical sensations, such as smells.

Wine appreciation must therefore start with thoughtful assessment of its nose, and this must not be rushed. The right shape of glass is also important to concentrate the evaporating wine molecules up towards the nose. The foul habit of smoking whilst dining will interfere with wine assessment, and after-shave and perfumes are more appropriate for clubbing than for enjoying good food and wine. I trust you should by now already realise that there is far more to wine appreciation than memorising some wine brand names and labels.

*Albert Cilia-Vincenti is a longstanding member of the Wine Society (1874) of the UK & founding committee member of Il-Qatra Wine Club (1999).*

# Professor Basant Puri to Talk at Malta Medical School about his Research on Depression, ME & ADHD

*An introduction by* **Albert Cilia-Vincenti**

*Professor Basant Puri has been invited to talk about his research on these brain function disorders by our University's Family Medicine Department and Department of Psychiatry. The talk will be delivered at the Medical School on Thursday 11th December. All doctors, pharmacists are invited to attend.*

Who is Basant Puri? Professor Sir Graham Hills describes him as a 'distinguished medical scientist who is a leader in the field of brain science, and whose researches are of the highest originality and offer new and sounder basis for the future diagnosis and treatment of depression'. Besides being a consultant psychiatrist, he is also a consultant to the Imaging Sciences Department of the Medical Research Council's Clinical Sciences Centre at the Hammersmith Hospital. He is also head of the Lipid Neuroscience Group of Imperial College.

A Cambridge graduate, Basant Puri recalls how, when he was training in psychiatry, he was struck by a lecture given by the now world famous psychiatrist Dr David Healy, on the many side-effects of antidepressant therapy, as he actively questioned the underlying theories about how depression occurs and how it should be treated - something not found in textbooks - and challenging prevailing medical wisdom.

After psychiatry and neuroimaging training, Puri came across Professors David Horrobin and Malcolm Peet's work on essential fatty acids to treat depression. Information available then, and subsequent research, pointed towards one particular marine omega-3 fatty acid, '*eicosapentaenoic acid*' (EPA), being head and shoulders above the others as a likely antidepressant. He set out to try EPA therapeutically as an antidepressant, and the initial astonishing results were followed up with trials confirming that EPA lifts even very serious depression.

He further discovered that EPA improves brain function overall. He believes that the human body has a particular need for omega-3 fatty acids and that a deficiency is likely to lead to many of today's common clinical problems. Western diet and lifestyle may have compromised our ability to make our own EPA. Factors such as caffeine, nicotine, stress hormones, saturated fats, trans-fatty acids and certain vitamin and mineral deficiencies may interfere with our bodies' ability to produce EPA and closely related omega-3 fatty acids. Now that this is understood, he recommends supplementation with EPA and other fatty acids, particularly if plenty of oily fish is not being consumed.

Professor Puri admits that the path to establish the therapeutic role of EPA has not been easy, with the reaction from many of his psychiatric colleagues regarding his EPA research ranging from sceptical to downright scathing. However, he is confident that EPA has been shown to work and that attitudes are slowly changing as evidence reaches a wider audience.

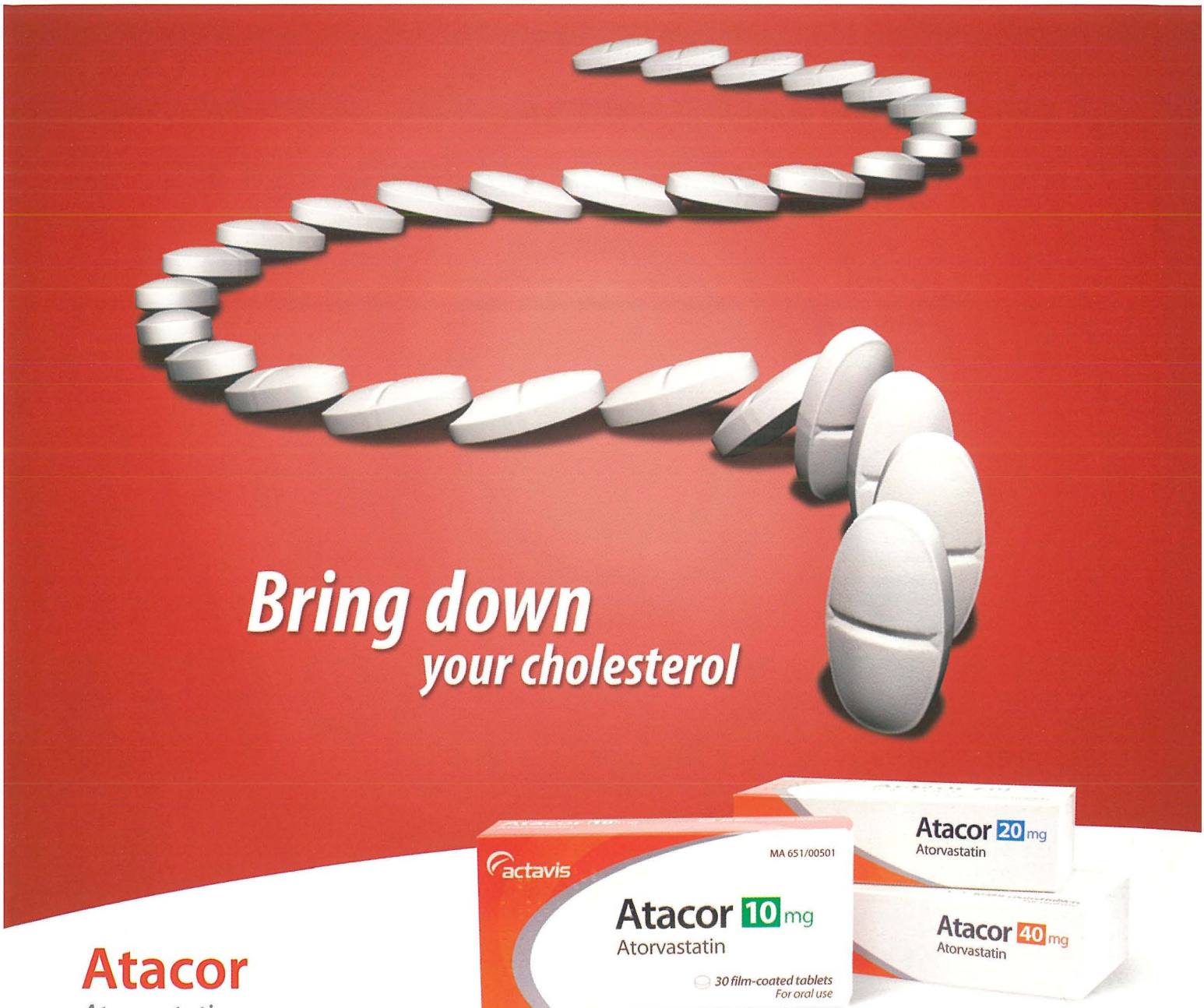
Depression and other mood disorders are characterised by reduced electrical brain activity ('circuit-board malfunctioning'), which is thought to be partly due to low levels of brain serotonin, noradrenaline and dopamine. Puri's theory is that neurons and neurotransmitters do not function properly because of an insufficient supply of EPA. He has demonstrated, with specialised MRI scanning, that these brain function disorders are accompanied by shrinkage of the grey cortex, and that cortical thickness recovery after a few months of EPA supplementation accompanies lifting of depression.

He believes that EPA enhances the brain's regenerative capabilities. Until recently, we thought that brain tissue was incapable of regeneration, but recent American experiments on rats demonstrated that neurons do regenerate in response to brain exercise. Interestingly, his MRI brain scans have demonstrated that pregnant women's grey cortex shrinks (possibly because the foetus is scavenging the mother's fatty acids for its own brain development) and then recovers its former thickness postpartum. This may well have something to do with pregnancy-related depression in some women.

Puri claims that the naturally-occurring fatty acid EPA has a strong scientific basis for its success in treating depression, whereas pharmaceutical antidepressant drugs do not. He stresses that all antidepressants have side-effects (including the new SSRIs), ranging from minor ones such as nausea, dry mouth and dizziness, to more distressing ones such as sexual function loss, to potentially life-threatening ones such as convulsions and heart disturbances. He adds that EPA can be taken safely with antidepressant drugs, but caution should be exercised in conjunction with anti-coagulant medication (fish oil has anti-coagulant properties). He believes EPA is a more reliable and scientifically sound natural alternative treatment for depression than St John's Wort, and that EPA is also useful in schizophrenia and in Huntington's.

Puri has also researched chronic fatigue syndrome/myalgic encephalomyelitis (ME), a complex controversial illness characterised by variable symptoms, including intense fatigue, muscle and joint pain, depression, poor concentration, disrupted sleep and headaches. There is no definite cause for ME, and triggers such as viruses and personal trauma have been blamed. He believes there is some link with depression, although which comes first, depression or ME, is unclear. He and his Hammersmith colleagues have studied ME patients' brains with MRI spectroscopy, and found a clear and significant chemical abnormality in these patients, which they didn't find in controls. The abnormality is in the phospholipid layer of neuronal membranes, the same problem found in depression. He believes ME results from viral or other influences that reduce essential fatty acids, and that EPA is essential to recovery in the great majority of patients.

*continues on page 27*







# Atacor

*Atorvastatin*

*10mg, 20mg, 40mg tablets*

*Lipid Reducing Agent*

**Composition:** Each tablet contains Atorvastatin calcium equivalent to Atorvastatin. **Therapeutic indications:** Atacor is used as a supplement to a change in diet for reduction of elevated total cholesterol, LDL - cholesterol, apolipoprotein B, or triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia (such as Frederickson's types IIa and IIb), when satisfactory results have not been obtained by a special diet or measures other than medication. In combination therapy with e.g. other LDL - cholesterol reducing medicinal products or if satisfactory results have not been obtained by other measures of reducing total cholesterol and LDL - cholesterol in patients with homozygous familial hypercholesterolaemia. **Posology and method of administration:** The patient should be placed on a standard cholesterol-lowering diet before receiving Atacor and should continue following this diet during treatment with Atacor. Doses should be determined individually according to the baseline LDL - cholesterol value, treatment objective and patient response. The usual starting dose is 10 mg once a day. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. The daily dose should be administered all at once and can be taken at any time of the day, with or without food. Treatment objectives for patients with a confirmed coronary disease or other patients at increased risk of ischemia are LDL - cholesterol <3 mmoles/l (or <115 mg/dl) and total cholesterol <5 mmoles/l (or <190 mg/dl). *Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia:* An appropriate dose for most patients is 10 mg Atacor a day. A response is evident within 2 weeks and maximum response is usually achieved within 4 weeks. The response is maintained during long term treatment. *Heterozygous familial hypercholesterolaemia:* The initial dose is 10 mg Atacor a day. Doses should be determined for each patient and adjusted at 4 week intervals up to 40 mg a day. Then the dose can be increased to either a maximum of 80 mg a day or else, 40 mg of atorvastatin once a day can be administered in combination with a bile acid sequestrant. *Homozygous familial hypercholesterolaemia.* In a clinical study of 64 patients, 46 of whom had homozygous familial hypercholesterolaemia, atorvastatin was administered in up to 80 mg doses. For these 46 patients the mean reduction of LDL - cholesterol was 21%. Patients with homozygous familial hypercholesterolaemia who had not been responsive to alternative treatments received atorvastatin of 10-80 mg doses a day concurrently with other blood lipid lowering treatment (e.g. other LDL cholesterol reducing medicinal products). *Patients with impaired renal function:* Renal diseases influence neither plasma concentration nor the effects of atorvastatin on blood lipids and therefore no dose adjustment is required. *Elderly:* Efficacy and safety of the use of recommended doses for patients over 70 years old are similar as for other adults. *Children and adolescents:* The use in children should be supervised by a specialist. Experience of the use of the medicinal product in children is limited and restricted to a small group of patients (aged 4 - 17 years) with serious hyperlipidaemia such as homozygous familial hypercholesterolaemia. The recommended initial dose for this group is 10 mg atorvastatin a day. Based on response and tolerance the dose can be increased to 80 mg a day. Information regarding safety with respect to maturation for this group has not been evaluated. **Contraindications:** Atacor is contraindicated in patients with a history of hypersensitivity to the active substance or to any of the excipients, in patients with an active liver disease or unexplained persistent elevation of serum transaminase levels where the elevation exceeds three times the mean upper limits, in patients with myopathy, pregnant and breast feeding women and women of child bearing potential not using contraceptives. **Special warnings and precautions for use:** *Liver effects:* Liver function tests should be performed before the initiation of treatment and periodically during treatment. Liver function tests should be performed if signs or symptoms of possible liver damage are observed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. In case of an elevation of transaminase levels exceeding three times the mean upper limit, dose reduction or discontinuation of treatment with Atacor is recommended. Atacor should be used with caution in patients who consume substantial amounts of alcohol and/or have a history of liver disease. *Skeletal muscle effects:* Like other HMG-CoA reductase inhibitors, atorvastatin can very rarely influence skeletal muscles and cause myalgia, myositis and myopathy which can evolve into rhabdomyolysis, which is a potentially fatal condition and is characterized by an elevated CPK value (exceeding ten times measured upper limits), myoglobinaemia and myoglobinuria, which can cause renal insufficiency. **Interaction with other medicinal products and other forms of interaction:** *Cytochrome P450 3A4 inhibitors:* Atorvastatin is metabolised by cytochrome P450 3A4. Interactions can occur during concurrent administration of atorvastatin and a cytochrome P450 3A4 inhibitor (e.g. cyclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Special precaution is required during concurrent administration of atorvastatin and these products because it can result in elevated plasma concentration of Atorvastatin. *Erythromycin, clarithromycin:* Concurrent administration of atorvastatin, 10 mg once a day and erythromycin (500 mg four times a day) or clarithromycin (500 mg twice a day), known cytochrome P450 3A4 inhibitors, resulted in a higher plasma concentration of atorvastatin. *P-glycoprotein inhibitors:* Atorvastatin and its metabolites are substrates of P-glycoprotein. P-glycoprotein inhibitors (e.g. cyclosporin) can increase the bioavailability of atorvastatin. *Itraconazole:* Concurrent administration of atorvastatin 40 mg and itraconazole 200 mg a day resulted in a threefold increase in the AUC of atorvastatin. *Protease inhibitors:* Concurrent use of atorvastatin and protease inhibitors which are known CYP3A4 inhibitors resulted in an increased plasma concentration of atorvastatin. *Grapefruit juice:* Contains one or more CYP3A4 inhibitors and can cause elevation in plasma concentration of medicinal products metabolised by CYP3A4. Drinking large amounts of grapefruit juice is therefore not recommended during atorvastatin treatment. *Cytochrome P450 3A4 inducers:* The effects of cytochrome P450 3A4 inducers (e.g. rifampicine or phenytoin) on atorvastatin are not known. Possible interactions with other substrates of this isoenzyme are not known, but should be considered in case of medicinal products with a narrow therapeutical index, e.g. class III antiarrhythmics, including amiodarone. *Gemfibrozil / fibrates:* The risk of atorvastatin induced myopathy can increase during concurrent administration of fibrates. *Digoxin:* Repeated administration of digoxin and atorvastatin 10 mg at the same time did not influence the steady state plasma concentration of digoxin. Digoxin concentration however increased by 20% during concurrent use of digoxin and atorvastatin 80 mg a day. Patients treated with digoxin should be monitored carefully. *Oral contraceptives:* Concurrent use of atorvastatin and oral contraceptives increased the concentration of norethisterone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses. *Colestipol:* Plasma concentration of atorvastatin and its active metabolites decreased (approx. 25%) when colestipol was administered with atorvastatin. However, lipidaemic effects were greater when atorvastatin and colestipol were administered together than when either drug was administered alone. *Antacids:* Concurrent administration of atorvastatin and oral antacid liquid formulations containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations by approx. 35%; reduction of LDL-cholesterol was however not altered. *Warfarin:* Concurrent use of atorvastatin and warfarin caused a minor decrease in prothrombin time during the first days of treatment, but returned to normal within 15 days. Nevertheless patients receiving warfarin should be closely monitored when atorvastatin is added to their treatment. *Phenazone:* Concurrent use of atorvastatin and phenazone for some time resulted in little or no visible effect on the clearance of phenazone. **Pregnancy and lactation:** Atacor is contraindicated in pregnancy and while breast feeding. Women of child bearing potential have to use effective contraceptive measures during treatment. Safety of atorvastatin use during pregnancy and lactation has not been established. **Effects on ability to drive and use machines:** Atorvastatin has no known influence on the ability to drive and use machines. **Undesirable effects:** The most frequent adverse effects that can be expected are symptoms of the gastrointestinal system, including constipation, flatulence, dyspepsia, abdominal pain, usually resolving during continued treatment. Less than 2% of patients had to discontinue clinical trials due to side effects related to atorvastatin. **Gastrointestinal disorders:** *Common:* Constipation, flatulence, dyspepsia, nausea, diarrhoea, *Uncommon:* Anorexia, vomiting. **Blood and lymphatic system disorders:** *Uncommon:* Thrombocytopenia. **Immune system disorders:** *Common:* Hypersensitivity, *Very rare:* Anaphylaxis. **Endocrine disorders:** *Uncommon:* Alopecia, hyper- or hypoglycaemia, pancreatitis. **Psychiatric disorders:** *Common:* Insomnia, *Uncommon:* Amnesia. **Nervous system disorders:** *Common:* Headache, dizziness, paraesthesia, hypoesthesia, *Uncommon:* Peripheral neuropathy. **Hepatobilary disorders:** *Rare:* Hepatitis, cholestatic jaundice. **Ear and labyrinth disorders:** *Uncommon:* Tinnitus. **Skin and subcutaneous tissue disorders:** *Common:* Rash, pruritus. *Uncommon:* Urticaria. *Very rare:* Angiodema, bullous eruptions (including erythema multiforme, Steven-Johnsons syndrome and toxic epidermal necrolysis). **Musculoskeletal disorders:** *Common:* Myalgia, arthralgia, *Uncommon:* Myopathy, *Rare:* Myositis, rhabdomyolysis. **Reproductive system:** *Uncommon:* Impotence. **General disorders:** *Common:* Fatigue, chest pain, back pain, peripheral oedema, *Uncommon:* Malaise, weight gain. **Overdose:** No specific treatment for Atacor overdose is available. In case of an overdose the patient should be treated symptomatically and supportive measures should be instituted if required. Liver function should be monitored and serum CPK values also. Due to its extensive binding to plasma proteins haemodialysis is not expected to increase atorvastatin clearance significantly.

**Marketing Authorisation Holder:** Actavis Group hf, Reykjavikurvegi 76-78, 220 Hafnarfjörður, Iceland. **Date of first authorisation or renewal of authorisation:** 27th March 2007.

**This medicinal product is subject to a medical prescription.**

For full prescribing information contact the local representative of the Marketing Authorisation Holder.

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# European Antibiotic Awareness Day

Antibiotic resistance is undoubtedly one of the biggest challenges facing modern healthcare. It impacts directly on our patients resulting in higher mortality and morbidity than equivalent infections caused by sensitive microorganisms. A major driver for the development of resistance has been shown to be antibiotic use. For this reason campaigns aimed to reduce resistance have over the past years focused on better antibiotic management. This year, the European Centre for Disease Control (ECDC) is launching a European initiative for Health which aims to increase awareness on the importance of proper consumption of antibiotics amongst health professionals as well as the general public. Key amongst these initiatives will be a yearly European Antibiotic Awareness Day (*http://antibiotic.ecdc.europa.eu/*) which will be celebrated on the 18th November of every year.

Locally, a conference on antimicrobial resistance in hospital care was held on 18th November 2008 at the Hotel Excelsior, Floriana. In addition, a symposium on antibiotic prescribing in community practice was held on 19th November in the Mater Dei Hospital auditorium. This meeting was targeted for community doctors and pharmacists. This event provided an opportunity to review issues of resistance in community-acquired infections and discuss possible avenues of approach relevant to the local circumstances.


In addition the local campaign will also address public opinion through a series of media events, dissemination of leaflets, posters and billboards.



# Update on Avian Influenza

*by* **Tanya Melillo Fenech** *MD MSc*
*Resident Specialist*
*Head, Infectious Disease Prevention and Control Unit*
*Department of Health Promotion and Disease Prevention*

There were no new human cases of avian influenza A (H5N1) reported to WHO since 10th September 2008.

A study done at Leicester University and published in the *New England Journal of Medicine* this year showed that a vaccination given against one strain of avian influenza 6 to 8 years previously, can 'prime' the immune system to give a rapid response with a booster shot within a week to fight another avian influenza strain. The research centred on a group of people who were given a vaccine against H5N3 strain of avian influenza between 1999 and 2001. Years later, they were vaccinated against the H5N1 strain of avian influenza and their immune system response was compared against a group who had not received earlier vaccination. The vaccine contained another ingredient called MF59 designed to boost its effectiveness.

After just 7 days, 80% of the 'primed' group had signs that their body was protected against H5 N1 compared with 20% of the 'unprimed' group. The earlier vaccine had not only offered protection against the original strain but laid the foundations for protection against other avian influenza strains.

## Seasonal Influenza

A study on the effectiveness of maternal influenza immunization in mothers and infants published in the *New England Journal of Medicine* last September found that among the 159 infants whose mother received the influenza vaccine there were only 6 lab confirmed influenza infections, as compared with the 16 lab confirmed influenza infection among the 159 infants whose mothers were in the control group. Those in the control group were given the 23-valent pneumococcal polysaccharide vaccine. This is compatible with a vaccine effectiveness of 63% (95% CI – 5 to 85%). In addition the influenza immunized group experienced a 29% (95% CI – 7 to 46%) reduction in infant respiratory illnesses with fever and a 42% (95% CI – 18 to 59%) reduction in the rate of infant clinic visits. It was estimated that 100 maternal influenza vaccinations prevented 7 and 14 cases of respiratory infection with fever in the mothers and babies respectively. The study showed also that the virus was circulating for at least 10 of the 15 months of observation.

Jansen et al in *Vaccine Journal* last August reported a retrospective nationwide cohort study in the Netherlands over 1992-2003, using mortality and viral surveillance data. It was found that routine influenza vaccination among Dutch elderly was statistically associated with a significant decrease in influenza-associated mortality, notably in those aged 65-69 years (relative risk of 54) but less in those aged 75 years and over.

In May 2003 during the 56th World Health Assembly (WHA), all EU Member States committed to the goal of attaining vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010 and to having mechanisms for monitoring the uptake in place. Presently 17.1% of the EU population are currently aged 65 years or older.

An article in *Euro Surveillance* last October reviewed data collection of vaccine coverage rates in the elderly in Europe. Data was only available in 19 out of the 29 EU Member States. >From these 19, only one country, the Netherlands, reached the WHA 2010 target of 75% coverage in the elderly and another, the United Kingdom, is just below this target at 74%. Nine countries met the 2006 target of 50%. However, the remaining eleven countries failed to pass the 2006 target of 50% coverage in 2006-7. Malta is one of the countries who as yet does not have a proper system in place to be able to collect the actual coverage rate of our elderly population and high risk groups.

# ORELOX®

## *Cefpodoxime*

### Broad spectrum oral 3rd generation cephalosporin

- An oral antibiotic for most community acquired infections
- Skin and soft tissue infections
- Upper and lower urinary tract infections
- Upper and lower respiratory tract infections
- Acute Otitis media


**Brief Prescribing Information**

**ORELOX Children and infants 40 mg/5 ml Composition** for 100 g: Active ingredient:Cefpodoxime proxetil 6.261 g quantity corresponding to cefpodoxime 4.8 g. 5 ml of the reconstituted solution contains 40 mg cefpodoxime. **Pharmaceutical form:** Granules for oral suspension. **Pharmaco-therapeutic class** Antibacterial antibiotics belonging to the beta-lactam family: cephalosporins **Therapeutic indications** This medicine is indicated in children for treatment of certain bacterial infections caused by susceptible organisms, such as bronchitis, sinusitis, tonsillitis, pharyngitis, pneumonia, ear infections, skin infections, urinary system infections. **Contra-indications:** Hypersensitivity to cephalosporins • In case of phenylketonuria, because of the presence of aspartame **Special Warnings and special precautions:** Hypersensitivity reactions are to be reported • Allergy to cephalosporins may be observed (in 5 to 10% of cases) in subjects who are allergic to antibiotics of the penicillin family. • If diarrhea occurs, it could be exceptionally symptomatic of pseudomembranous colitis • Because of the presence of lactose, sorbitol and saccharose, this medicine should not be used in patients with fructose intolerance, congenital galactosemia, glucose and galactose malabsorption syndrome, lactase deficiency or sucrose isomaltase deficiency. **Precautions** • In case of severe renal impairment, it may be necessary to adjust the dosage according to creatinine clearance • In newborn infants under 2 weeks of age, this medicine should not be used • Since this medicine contains 66.55 mg of sodium per 50 ml vial, this must be taken into account in persons following a strict low-salt diet. • Since this medicine contains 2.17 mg of potassium for a 5 ml dose of reconstituted suspension vial, this must be taken into account in persons following a low-potassium diet. • This medicine can produce a false positive reaction in certain laboratory tests (screening for glucose in the urine with reducing agents, and Coombs' tests). **Interactions with other drugs and other forms of interactions** Antacids of the mineral type and H2 blockers such as ranitidine, which cause an increase in gastric pH, should be taken 2 to 3 hours after Orelox administration. **Pregnancy and lactation:** Not Applicable. **Effects on ability to drive and to use machines:** Not applicable. **List of excipients liable to produce some risks in some patients** Lactose, saccharose, sodium, aspartame, potassium, sorbitol. **Dosage** The usual dosage in children is 8 mg per kg per day, in 2 intakes separated by a 12-hour interval. In patients having severe renal impairment, the period between each administration must be adjusted. **Administration:** Oral use. Take the suspension during meals. **ADVERSE REACTIONS:** Mainly:- Diarrhea, vomiting, abdominal pain. - An extensive cutaneous eruption, angioedema. More rarely: - gastrointestinal manifestations rare cases of enterocolitis with bloody diarrhea have been reported as well as rare cases of pseudo-membranous colitis - Hepatic manifestations: Moderate rise in liver enzyme levels - Allergic manifestations: Skin eruptions, pruritus, urticaria and anaphylactic shock. - Skin manifestations: Miscellaneous skin rashes localized bullous eruption, erythema multiforme, Stevens-Johnson syndrome and Lyell syndrome. - Headache. - Sensation of dizziness. - Moderate rise in blood creatinine. - Hematologic manifestations: Decreased hemoglobin level, thrombopenia, neutropenia, hypereosinophilia, exceptionally agranulocytosis. **STORAGE:** Store below 25 °C. After first opening, the reconstituted suspension can be used for 10 days if stored between 2 °C and 8 °C. Keep out of the reach of children. **Marketing Authorization Holder:** Sanofi-Aventis Malta Ltd. Triq Kan. K. Pirotta B'Kara BKR 1114 Malta. **MA Number:** 082/02002. **PRESCRIPTION ONLY MEDICINE. MT-CEF-08-10-01 For full prescribing information, please contact the MA holder.**

sanofi aventis
Because health matters

# The use of Ethics Matrices

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

The PUME matrix helps us define 'what are we discussing'. In a moral debate we often bring in many arguments, some of which have to do directly, and others indirectly with the main moral issue at hand. Moreover the moral issue may lead to other ethical choices and to areas or issues of which we are unsure. In order to clarify one's thinking, in teaching and in moral debate, it is useful to distinguish therefore the main moral argument at hand, for example, sale of organs, from the pragmatic moral issues which arise – which indeed can have weight on the outcome. Then there are other ethical choices to be made – are there exceptions when we can tolerate the sale of an organ, for example if it is put as a condition in one's will? There are areas which we are unsure about – unsure whether they form part of the main moral argument or are more pragmatic such as autostimulation to produce a sample of sperm, as an argument against Invitro Fertilization. PUME stands for Pragmatic, Moral, Unsure and Ethical[1].

The four main areas therefore are:
**1.** The central MORAL question being discussed.
**2.** PRAGMATIC moral issues related to the central moral question.
**3.** Areas in which we are UNSURE between the above.
**4.** Other ETHICAL outcomes or choices related to this issue.

| | |
|---|---|
| **PRAGMATIC** | **UNSURE** |
| **MORAL** | **ETHICAL** |

**Figure 1:** *PUME Matrix*

We see that areas 2, 3, and 4 can all have an influence on the central moral question. This means that although we can find nothing inherently wrong with the central issue, the other three areas can have enough weight to make it overall prohibitive, as we shall see. Conversely, the central issue may be inherently wrong, for example the use of animals in experiments, but under certain circumstances, and because of the benefits, we allow it. Clarifying areas 2 – 4 is important as the reasoning may change in time. Thus we tolerate pollution to have cars, but if cars exceed a limit, the pollution may reach intolerable levels, or indeed we may have created other problems, such as congestion. We then revisit the central argument.

Having a matrix with these four areas, allows for better clarification in thinking and discussion. The matrix has indeed been used in group discussions both for teaching and public debates and can be used by a facilitator to focus the argument. One may, for instance, say, 'yes, indeed, that is an important point. It is perhaps a pragmatic moral argument, which although important, is not the main issue we are discussing; it is more of an outcome of the issue, which if resolved, will still leave us having to answer what we are debating here. Let us put it under Pragmatic Moral Issues.'

The matrix is useful insofar as it helps one distinguish between the true moral arguments and those which can or may be 'resolved'. This helps one distinguish in turn what are the true areas of conflict, where there is a difference in values, and areas of potential dispute, which if resolved, can help move one forward. One has to keep in mind that we may resolve a hundred disputes without resolving the main conflict, given that the conflict has to do more with a difference in values. To illustrate this by an external example, one can resolve many disputes between the Jewish and Palestinian states, and yet the main conflict between them remains. On the other hand, we may not really have a strong objection to the moral issue *per se*, but what matter more are the other moral issues which are raised. These are the 'pragmatic issues'. This is clearly illustrated by the cases for Invitro Fertilization and that of Organ Transplantation described below.

The reason for putting them in a matrix is two-fold. A matrix makes it easier to picture a problem. One can separate the arguments and put them into perspective. This can even be done in one's mind, since it is simple. Conversely, the columns on the left hand side are the main moral arguments, whilst the columns on the right are outcomes and choices with which we still have to deal. On the other hand, if we look at the matrix as rows, the upper row deals with moral issues external to the problem at hand, whilst the lower row is more inherent to the problem. Even if some ethical choices are not the main issue at hand, they are a direct result of the moral issue.

In the example of sale of organs for transplantation, the real issue is the morality of sale of organs; abuse of sale, or exploitation are pragmatic moral issues, which albeit can have an overall weight and become themselves the moral issues to decide the fate of the moral issue being discussed, are not in and of themselves the central moral issue – sale of organs. Conversely, with IVF, the fact that IVF can result in children with defects is indeed a moral issue, but a pragmatic one. If we resolve it, we are still faced with the moral issue of whether IVF is a morally good thing. People may then focus on the real discussion.

The matrix may or may not be useful to some, however it does have the advantage of clearly defining what we are talking about and at least agreeing on what is at stake and what is the true moral issue and what is not. Some may feel that separating the moral issue from the other moral issues it raises is not taking a holistic approach. This is not so, as the matrix does not prohibit the discussion and the weight that the pragmatic issues raise. Indeed it teases them out so that they may be treated separately in order to finally contribute (holistically) to the main argument at hand. This is certainly the case for sale of organs, which is prohibited because of other moral issues it raises - such as putting at a disadvantage those who need money or people from third world countries. So even if one decides there may *prima facie* be nothing seriously wrong with selling an organ, the consequences cannot be ignored and therefore on further reflection makes this sale unethical.

[1] The PUME matrix was devised over several years of public debate and reflective teaching in bioethics with students of the University of Malta, and not least after the training imparted in Malta in adult learning, by the RCGP. I had been using the argument of separating the main argument at hand, from those other moral issues that arise from the main one, in order to create less confusion and to focus on the argument at hand.

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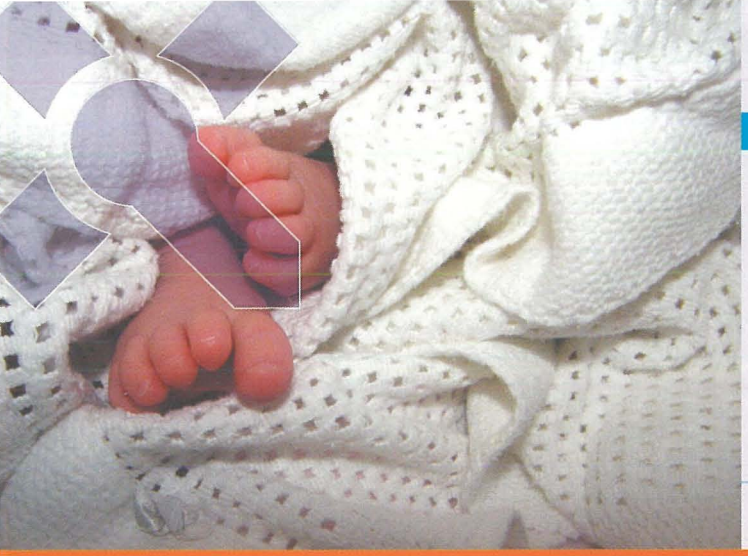




# HOPE for the

by **Marika Azzopardi**

*Dr Karen Vincenti MD is a busy mum and doctor. With a background covering Public Health, Family Medicine, Infectious Disease and Environmental Health , it surprising to find her involved in an association such as HOPE. But being one of the founding members of GOL – the Gift of Life foundation – together with her husband Paul Vincenti, makes her an ideal candidate.*

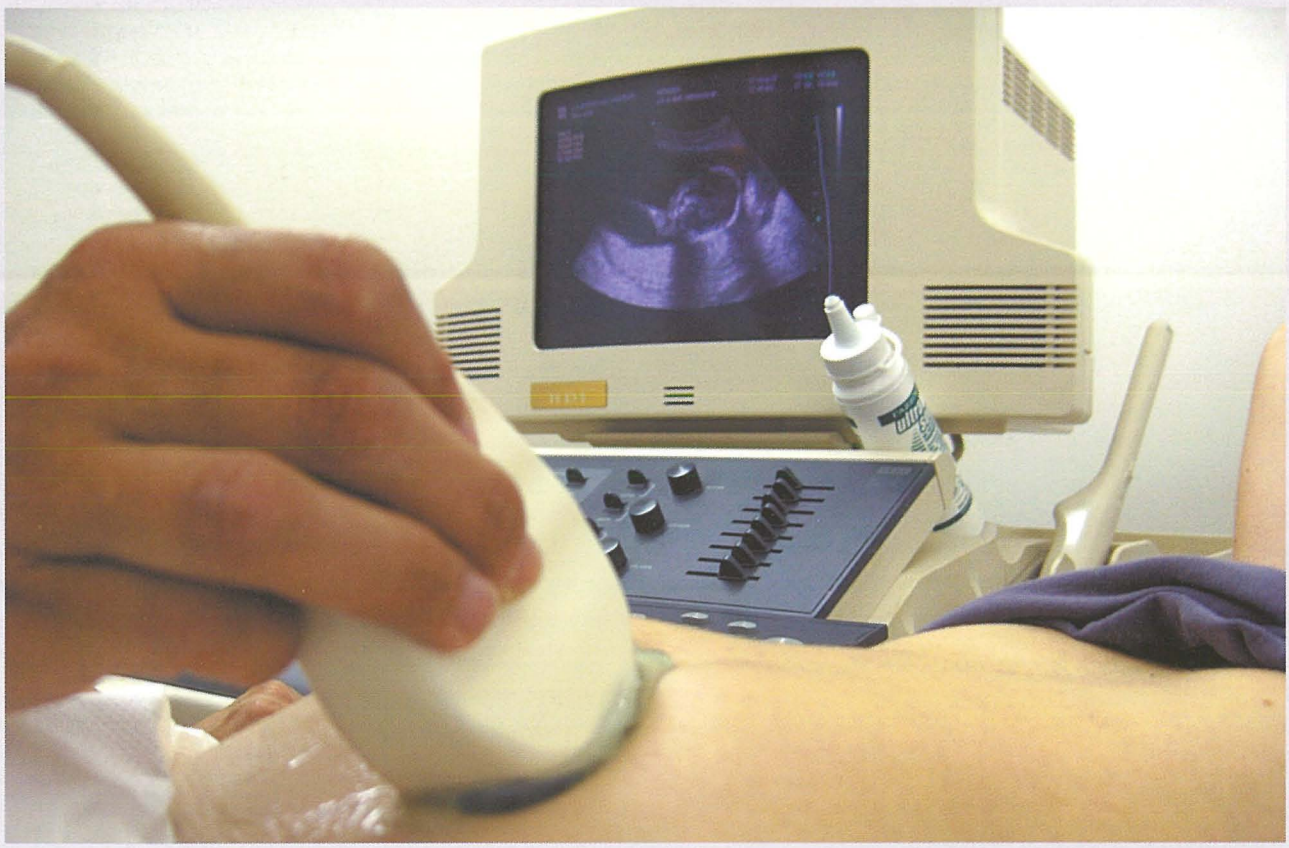
"As a group we were always concerned about the importance of education and support in this situation. When several women in crisis pregnancies requested our specific help, HOPE was born in 2006 – as a Crisis Pregnancy Support Service." Some time later PAIS – Pro-Life Awareness in Schools – was set up as the educational wing of GOL.

HOPE's role is simple to understand. Whereas GOL lobbies for pro-life action, HOPE supports and offers practical help, education and information to women in distress at a delicate moment. Facing an unexpected pregnancy is not a simple situation.

"I have been actively involved in clinical work at the Infectious Diseases Clinic for a number of years and it is there that I became also concerned with the lifestyle many women lead. Not only do they expose themselves to a high risk of infectious sexually transmitted diseases – but they also risk unplanned pregnancies. I am familiar with talking to people about these risks so when women turn up at HOPE, at some point I often suggest they undergo screening for STDs."

One of the most stringent concerns in her weekly clinic work revolves around HIV which, Dr Vincenti says, has taken an alarming upward surge. This intensifies her belief that education has to be directed meaningfully. "In an ideal scenario, crisis situations should be prevented. We have seen the youngest mum to approach HOPE to be in her early teens but women who consult us are not all teenagers – we even get women in their forties. An unexpected pregnancy may come at any moment in a woman's life whether she is single, married, having relational difficulties, one-night stands, extra-marital affairs."

Dr Vincenti mentions a phenomenon that has seen Maltese women



# Unborn

*Dr Karen Vincenti*


becoming increasingly involved with foreigners, including considerable numbers of African men. When these women suspect they have become pregnant through an 'illicit' relationship with a dark-skinned person, many times further panic sets in as they may also be concerned about the skin colour of the child.

*Advising women in such situations means threading a fine line between being pro-life and being anti-abortion. What is HOPE's stand?*

"HOPE is part of a pro-life organisation and we do our best to help both woman and child. Many things may push a woman to the extreme of considering an abortion and I am quite sure that no woman would willingly go for an abortion if she could avoid it, no matter her situation, values, or religious belief. At HOPE we offer a listening ear, information, support and a non-judgemental environment to allow the pregnant woman reach an informed decision away from all the pressures she may be experiencing at the time. Most women who seek our help are relieved to discover that no matter how difficult their circumstances may be there is hope and support free of charge that will make it possible for them to keep their child"

Fear of a new situation, fear of failure to cope, fear of life-changing circumstances – these all add up to the pressure of taking the right decision that will mark a woman's future. Dr Vincenti says that amongst the women who turned up for help at HOPE, there were some who had already experienced an abortion. "Women usually go to the UK or Sicily to abort."

Up until recently Dr. Vincenti served as the first point of contact for women requesting help. The core team, now made up of 12 women, mostly professionals–support the women in crisis according to their specific needs and of course, our limitations. We often refer women to other specialists according to need. "Several gynaccologists and other professionals have also offered their services to our group. We do have an ultrasound machine, which was donated to us, on our premises but this is not used for diagnostic purposes and does not replace the obstetric visit and scans."

Dr Vincenti's role within HOPE is also and ultimately a co-ordinating one. HOPE is regularly offered supplies which could come in handy to women preparing to deal with raising a child. "Our stores are crammed with stuff that we donate to expectant mums – maternity and baby clothes, prams, cots, sterilizers, breast pumps, playpens, hi-chairs – the lot. We usually prepare the baby's layette and the mother's hospital bag with all that is needed and also see how we can help her cope with her new situation. There are other similar support groups working abroad such are LIFE in the UK, Human Life International in the US and Be'Ad Chaim in Israel. We have received much help from these quarters. Ultimately crisis pregnancy is not only a Maltese issue – it is an international one concerning all women."

HOPE

*HOPE welcomes any help with acquiring vitamins, formula milk, nappies, maternity and baby items or anybody wishing to volunteer professional service. Contact weekdays 14.30 – 18.00 or Saturday mornings before 13.00 on 21418055 or email hope@lifemalta.org. Check out www.lifemalta.org*

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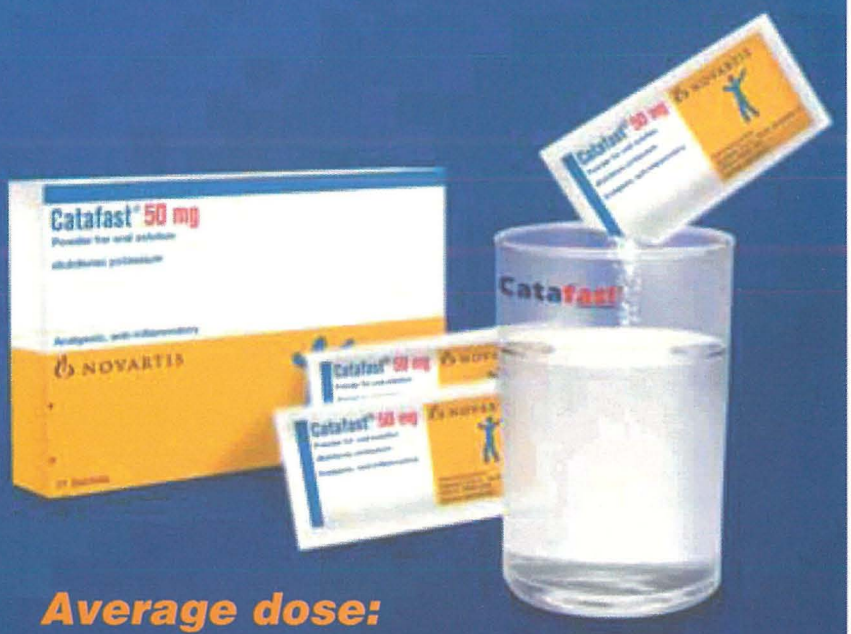


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References

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# Why are some cancers missed on mammography

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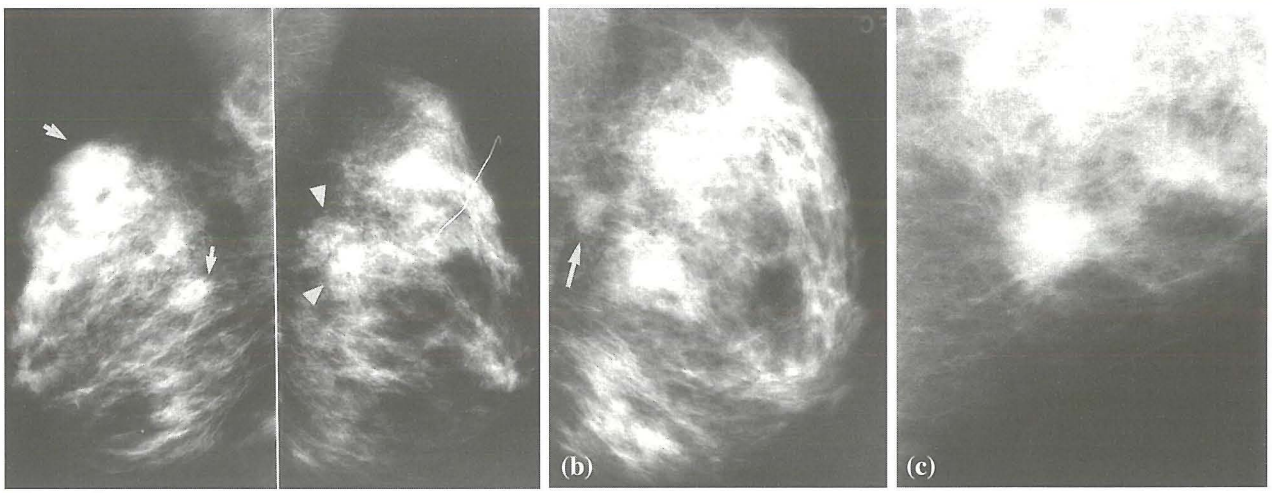


**Figure 5.** *Creative positioning for lesion detection. (a) Bilateral mediolateral oblique mammograms show dense parenchyma with well-defined masses (arrows) and a focal irregular density superoposteriorly on the right side (arrowheads). The well-defined masses proved to be cysts at US. (b) On a right lateromedial mammogram, the irregular density (arrow) has moved upward, a finding that indicates a medial location. At lateromedial mammography, the medial aspect of the breast is closer to the film and can therefore be better evaluated. (c) Spot magnification mammogram (right cleavage view) demonstrates a spiculated mass. Pathologic analysis revealed invasive ductal carcinoma.*

Poor positioning or technique may also result from chest wall deformities and patient respiration during the mammographic exposure. Sometimes a lesion may be located outside the normal field covered by mammography. Standard mammographic images are designed to try to include as much of the breast tissue as possible in planes and 90degrees to each other (mediolateral oblique and craniocaudal: MLO and CC). In these cases, one should obtain mammographic images in positions that differ from the standard view in order to include any palpable nodule (Figure 4); this is sometimes referred to a creative positioning. Emphasis on the upper outer quadrant, which demonstrates the greatest proportion of breast cancers, is necessary.

continues on page 26



# The commonly held image of women with osteoporosis as fragile and hunched over is outdated

continued from page 8

Other barriers to compliance include the frequency and method of administration. The Timeless Women report found that lack of compliance with medication can be very significant. In fact 7 out of 10 women admitted that they have missed a dose. There are a number of factors leading to non-compliance, including:

- Side-effects
- Confusing treatment instructions
- Perception that treatment is ineffective / do not notice results
- Treatment inconvenient and interferes with day-to-day life
- Believe they are not at risk of fractures

While both the women with osteoporosis and doctors surveyed appear to be relatively satisfied with current osteoporosis treatments, they both agree that treatments with less frequent dosing would be beneficial and more convenient.

Almost three out of four women with osteoporosis believe that treatments with a less frequent dosing schedule would suit their lifestyle more. Despite a range of treatment options available, less than half of women with osteoporosis could remember their doctors discussing alternate treatments with different administration frequencies.

Although the myth of 'frail and fragile' does not apply, much needs to be done. Women with osteoporosis and their doctors should work together to ensure they fully understand each other and that the needs and lifestyles of women with osteoporosis are taken into account.

Today women over the age of 55 continue to lead full, active and challenging lives, maintain their independence, and continue to contribute to their families and society.

# Why are some cancers n

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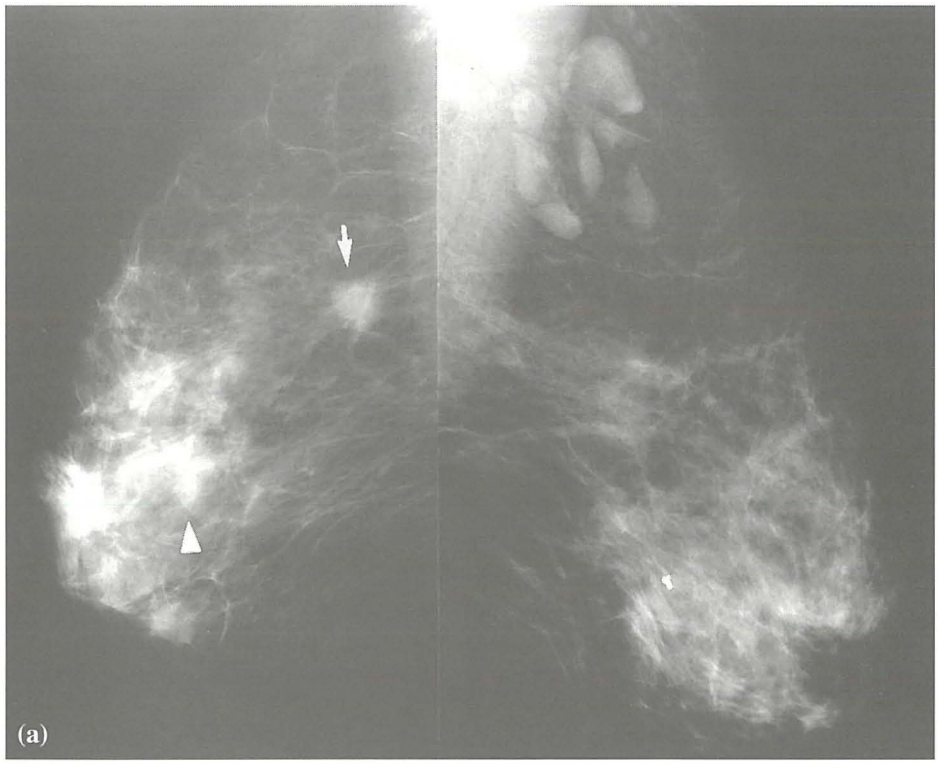
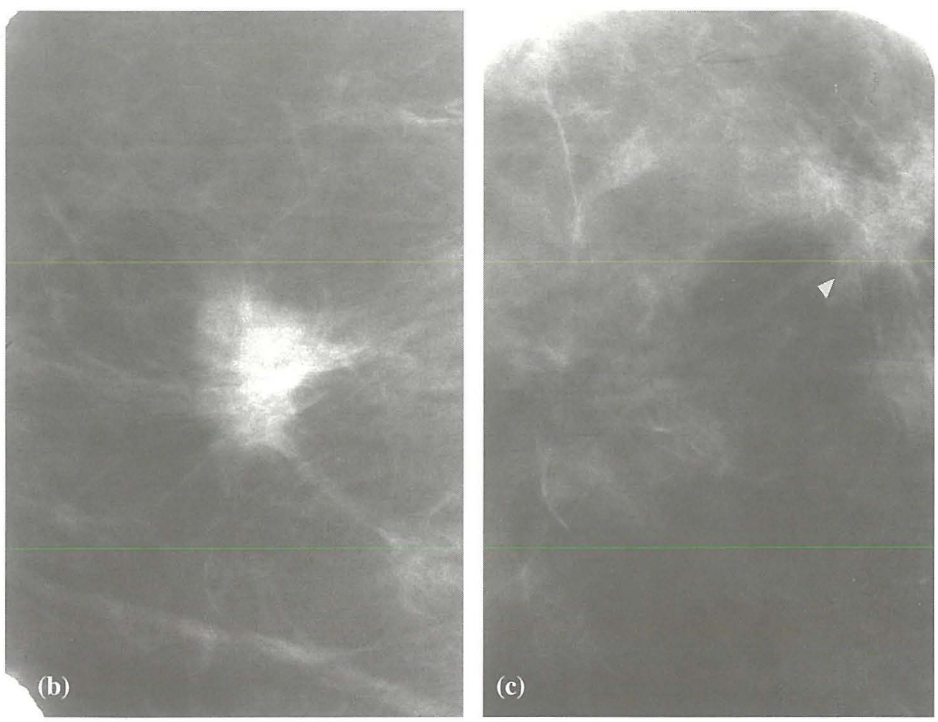



**Figure 6.** *Mirror image interpretation. (a) Bilateral mediolateral oblique mammograms reveal an irregular mass posteriorly on the left side with a highly suspect appearance (arrow). In addition, a subtle distortion is noted more inferiorly (arrowhead), a finding that becomes more evident with mirror image interpretation. (b, c) On left craniocaudal spot compression mammograms, the posterior (b) and anterior (c) lesions demonstrate a spiculated appearance (arrowhead in c). Pathologic analysis demonstrated multicentric invasive ductal carcinoma.*




Special view including rolled views, spot views and views with skin markers aid visualisation of mammographically difficult lesions (Figure 5).

Lack of perception of an abnormality that is present, incorrect interpretation of a suspect finding, subtle features of malignancy, or a slowly changing malignancy may all lead to a cancer being missed or detected late. Breast cancers are easily missed when they appear as focal areas of asymmetry or distortion (eg, invasive lobular carcinoma) or when their appearance suggests a benign cause (eg, medullary and mucinous [colloid] invasive ductal carcinomas, which usually manifest as mostly well-defined masses. Mirror image interpretation of mammograms, with corresponding images of the right and left breast being placed side-by-side, helps with detection of breast asymmetry (Figure 6). Ultrasound is very useful in such cases and if this does not explain what is seen on mammography, a biopsy must be performed.

Another special circumstance that can present a perception problem involves a patient with a palpable node in the axilla that is evaluated with biopsy and represents metastatic adenocarcinoma, likely of breast origin. The primary breast cancer may be occult or very subtle at mammography (Figure 7).

In conclusion, although mammography is the standard of reference for the detection of early breast cancer, cancers may be missed. To reduce the possibility of missing a cancer, the following steps

# issed on mammography

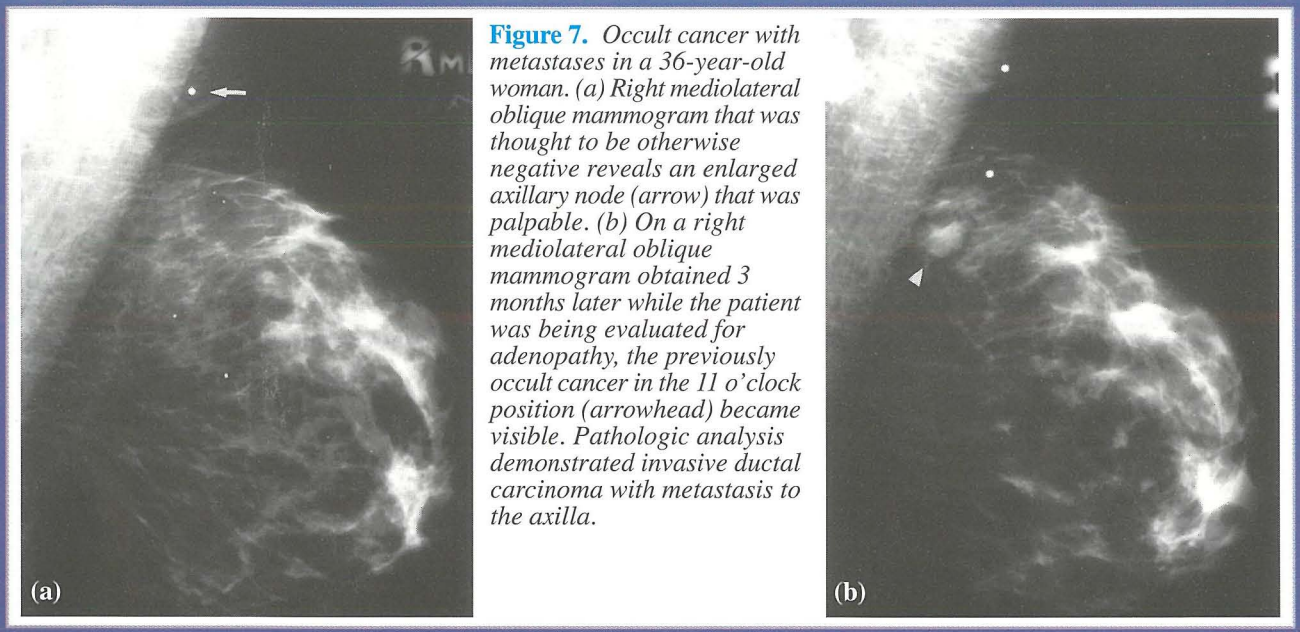



**Figure 7.** *Occult cancer with metastases in a 36-year-old woman. (a) Right mediolateral oblique mammogram that was thought to be otherwise negative reveals an enlarged axillary node (arrow) that was palpable. (b) On a right mediolateral oblique mammogram obtained 3 months later while the patient was being evaluated for adenopathy, the previously occult cancer in the 11 o'clock position (arrowhead) became visible. Pathologic analysis demonstrated invasive ductal carcinoma with metastasis to the axilla.*

are required when interpreting mammographic findings:

1. Do not rely on screening views alone to diagnose a detected abnormality; complete the evaluation with diagnostic mammography.

2. Review clinical data and use US to help assess a palpable or mammographically detected mass.

3. Correct positioning and technical requirements to optimize image quality.

4. Be alert to subtle features of breast cancers.

5. Compare current images with multiple prior studies to look for subtle increases in lesion size.

6. Look for other lesions when one abnormality is seen.

7. Judge a lesion by its most malignant features.

Dr Pierre Vassallo can be
reached at the DaVinci Hospital
on 21 491 200 or by email on pvassallo@davincihospital.com.mt



# Professor Basant Puri to Talk at Malta Medical School about his Research on Depression, ME & ADHD

*continued from page 16*

Increasing numbers of children and young adults are being diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD), and the best available treatment for many years has been powerful drugs that help control (but not cure) the worst symptoms. He feels that the potential side-effects of these drugs are worrying and the long-term consequences unknown, facing doctors, parents and adult sufferers with a terrible dilemma. Puri presents a very different way of looking at ADHD, and his starting point is the brain chemistry basis of behaviour and the many factors that influence this. By understanding behaviour at this level, he argues, it is possible to see how hyperactivity can be reduced and concentration improved in a natural way that is in tune with individual needs. He has been involved in major studies that demonstrate the effectiveness of a completely natural way to treat ADHD.

Prof Puri has published three paperbacks on the natural treatment of depression, ME and ADHD respectively, for use by both doctors and the general public. His invitation by our University's Family Medicine Department and Department of Psychiatry to talk at our Medical School should benefit our practitioners.

*Professor Cilia-Vincenti is a former London and Malta University teacher of diseases mechanisms. He is presently a consulting surgical pathologist, and represents Malta on orphan diseases at the European Medicines Agency. He has a longstanding interest in natural medicine.*

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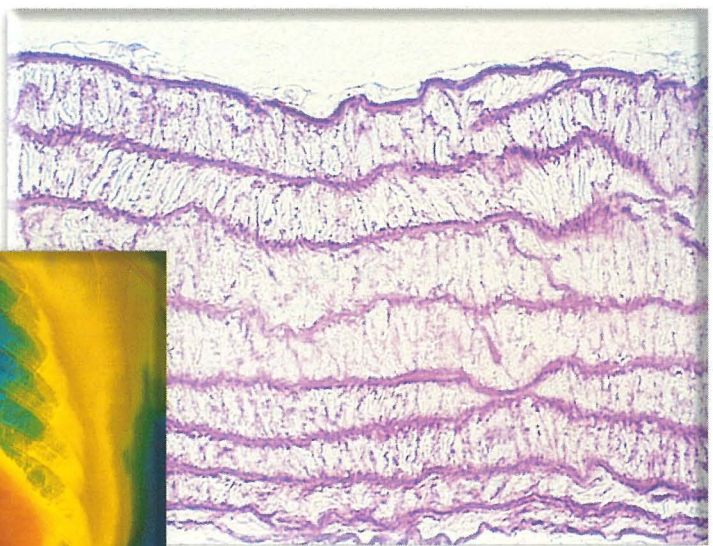
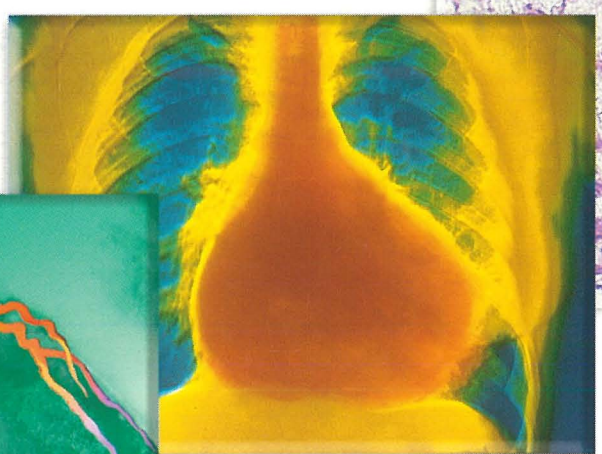
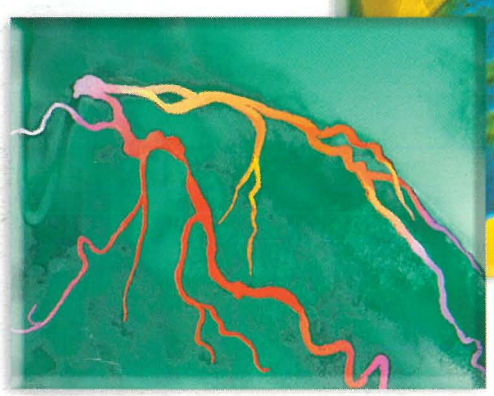


Hypertension[1,2]



Heart failure[3,4]



Stable coronary artery disease[5]

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