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12th Anniversary Edition

NEWSPAPER POST

TheSynapse

The Medical Professionals' Network

MEDICAL IMAGING

Pancreatic Cancer

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Pancreatic cancer is the fourth leading cause of death from cancer in the developed world. It has a dismal prognosis, with a mortality rate similar to its incidence.

The overall 5-year survival rate is less than 5%. Early diagnosis and resection remain the only potential cure, but only a minority (5–30%) of tumors are detected when they are still resectable. However screening has not proved to be effective in the general population and is not recommended.

Spiral Computed Tomography (CT) is the best technique currently available for detecting and staging pancreatic cancer. MRI is useful for equivocal cases and allows better visualisation of the common bile duct through MRCP (MR Cholangio-pancreatography), which may be helpful in operative planning. Ultrasound is often the first exam to detect a pancreatic cancer in those patients presenting with jaundice, but more accurate staging with Spiral CT is required to plan treatment.

Spiral CT technology has seen major advances over the past 15 years with progress from single slice to multislice techniques and ultrashort rotation times, with the result that large areas of anatomy can be imaged with exquisite detail in a relatively short breath hold. Power injectors are now utilized to administer timed bolus injections of contrast material, which allow imaging at different phases (arterial, venous and delayed) of organ perfusion. Carefully timed scan acquisition maximizes the difference in enhancement between the neoplasm and the pancreatic parenchyma and allows accurate local and distant staging. In addition, angiographic display of the local venous and arterial anatomy and TNM staging data (not usually used in radiographic reporting) are provided by spiral CT, which are crucial to surgical planning and are important for deciding on optimal therapy and neoadjuvant therapy.

During the late arterial phase of perfusion, the normal pancreas shows marked enhancement (figure 1), and imaging during this phase maximizes attenuation differences between the hypovascular tumor and the surrounding hypervascular normal parenchyma (figure 2). Usually, the tumor can be clearly seen against the enhanced background pancreatic parenchyma.

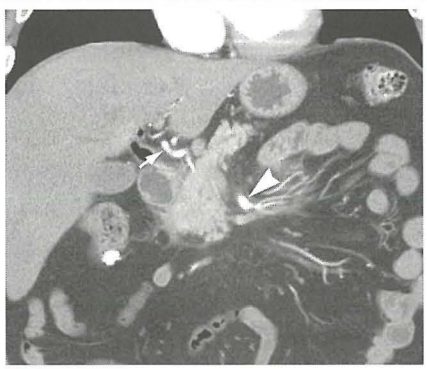


Figure 1. *Coronal reformatted pancreatic parenchymal phase image shows intense enhancement of the normal pancreas. Note the excellent enhancement of the common hepatic artery (arrow) and the superior mesenteric artery (SMA) (arrowhead).*

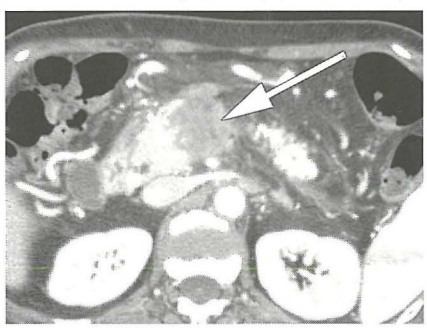


Figure 2. *Contrast-enhanced CT scan shows a large, locally unresectable adenocarcinoma of the pancreatic head (arrow). Note the difference in attenuation between the tumor and the avidly enhancing normal pancreas.*

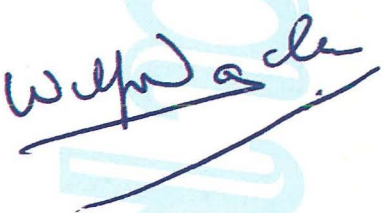
continues on page 2

Editor's Word

This issue marks another milestone in the history of TheSYNAPSE. Twelve years ago, TheSYNAPSE was born at the Malta Medical School. Little knowing whether we will reach our goals (but with a firm belief that we will), we have set on an ambitious project to provide a comprehensive set of tools and resources for all Maltese medical professionals. Looking through the documents and drafts (or dreams) of 1996, we are proud that we have managed to achieve many of the targets we dreamt of back then.

Today, we are pleased to offer a range of products and services for all members. It is however the contribution and interaction between members and stakeholders that is key to our success. It is this reason why we take this opportunity to thank all members and contributors for being part of the success story.

The future is exciting. The pipeline of products and service in development is very encouraging and we look forward to the future with confidence to build a better future together.



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Pancreatic Cancer

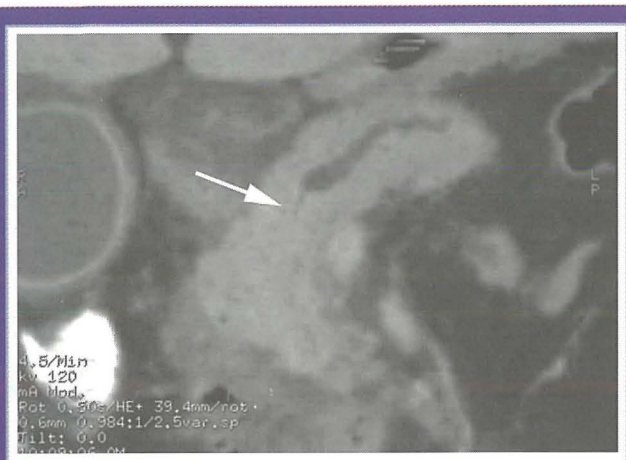

Figure 3. *Abrupt cut-off of the pancreatic duct (arrow) in the region of the neck of the pancreas. No mass was visualized in the pancreas at CT.*

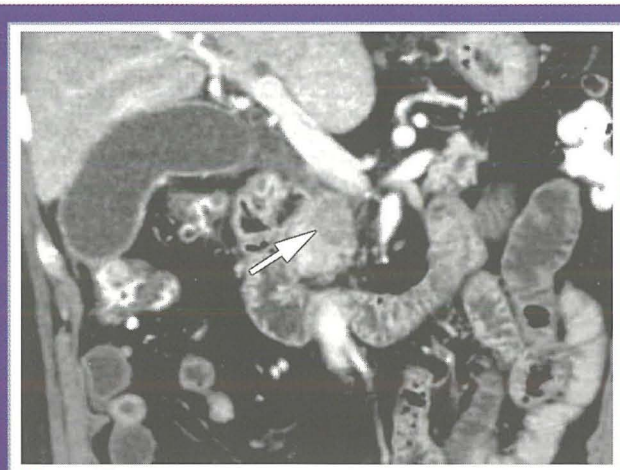

Figure 5. *Coronal reformatted pancreatic parenchymal phase image shows a focal hypoattenuating tumor (arrow). Whipple resection confirmed a T2 tumor.*

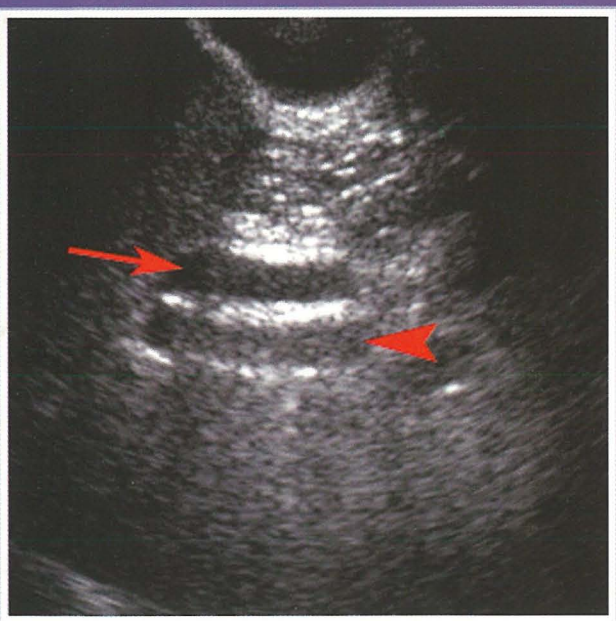

Figure 4. *Double duct sign seen on ultrasound with a dilated common bile duct (arrow) lying anterior to the portal vein (arrowhead).*

Secondary signs of malignancy such as pancreatic ductal or biliary dilatation or vascular occlusion can also be used to aid in tumor localization. About 10% of pancreatic adenocarcinomas have the same attenuation as background pancreatic parenchyma, making diagnosis more difficult. In such cases these secondary signs can be extremely useful (figure 3). The 'double duct sign', best seen on ultrasound (figure 4), is a reliable indicator of an obstructing lesion, although it is not specific for pancreatic adenocarcinoma; this is caused by obstruction of the distal pancreatic and common bile ducts, which are therefore seen as two adjacent dilated ducts.

Staging of pancreatic cancer follows the TNM classification (Table 1). Resectibility is staged according to size of the tumor and presence of nodal or extranodal metastases (Table 2). Most patients in whom resection appears to be viable at radiologic assessment will undergo laparoscopy prior to surgical exploration to rule out small peritoneal implants or liver disease, the presence of which precludes curative resection.

Approximately 90% of pancreatic adenocarcinomas manifest as a focal mass, with the remainder manifesting as more diffuse involvement. Radiologic imaging is highly sensitive for assessment of the T stage. T1 and T2 tumors are distinguished on the basis of size, and this assessment can usually be accurately made on the basis of spiral CT imaging (figure 5).

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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.
2. Novartis Europharm Ltd. Eucreas® Summary of Product Characteristics 2008

Eucreas® vildagliptin/metformin

GAL Ad2 09/08 MT

A practical and comprehensive overview of PET/CT – Part I

by **Mark Anthony Aquilina** *MD CCST*
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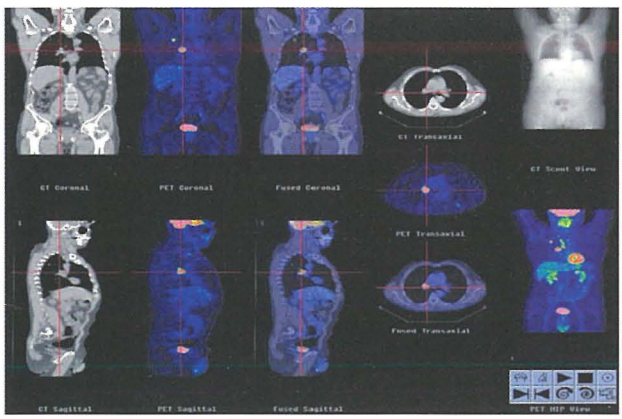
Like other nuclear medicine procedures, positron emission tomography (PET) differs from other imaging modalities in that it demonstrates physiological function of the system being investigated rather than anatomy. Tracer distribution and concentration is followed, hence allowing doctors to monitor the various cellular and molecular events taking place. A nuclear physician has the advantage of being able to interpret the superimposed images of a PET and a computed tomography (CT) scan concomitantly. This gives specialists much more confidence in writing definitive PET/CT reports: adding metabolic to anatomic data is synergistic with obvious advantages over stand-alone CT, or even stand-alone PET.

PET/CT involves an intravenous injection of radioactive tracers labelled with a positron emitting isotope. A positron may be considered to be an elementary particle with the same mass and magnitude of charge of an electron but exhibiting a positive charge, or simply a positive electron. Contrary to what many might think, PET does not detect positrons directly. It uses important features of positron 'annihilation' to determine their spatial location (see below).

It is curious that CT was originally integrated with PET for another fundamental reason besides the obvious diagnostic gain, as explained in the second part of this article. More advances are in the pipeline. Improved detectors and technology, PET/MRI and new tracers are being developed. This three part scientific overview is representative and by no means exhaustive. PET/CT will be justified as a contemporary, upcoming and indispensable imaging modality.



Dual-modality: a nuclear physician has the advantage of being able to interpret a metabolic image of a PET scan concomitantly to the anatomic data from a CT scan (image courtesy of HSR, Milano).

PET/CT tracers: The basics

In the synthesis of an ideal tracer, chemists must take into consideration that the label should not significantly change the biological properties of the parent molecule (transport, affinity with target, elimination). In fact PET/CT tracers most often comprise Carbon-11 (^{11}C), Nitrogen-13 (^{13}N), Oxygen-15 (^{15}O), and Fluorine-18 (^{18}F), all radioactive isotopes of elements that are easily incorporated by direct substitution into naturally occurring biomolecules. Substitution of ^{11}C for ^{12}C does not alter reaction times or mechanisms of the molecule. A similar situation exists for ^{13}N and ^{15}O; ^{18}F can often be substituted for a hydroxyl group on a molecule, or placed in a position where its presence does not significantly alter the biological behaviour of the biomolecule.

The positron-emitting isotope chemically linked to the molecule of interest must not dissociate easily, otherwise it is the isotope that is 'followed' by PET/CT rather than the tracer. Moreover, these tracers have the 'advantage' of a relatively short half-life with a consequent decreased radiation exposure to patients. On the other hand, time is critical: tracers must be synthesized and imaged within a time frame compatible with the half-life of the isotope. Ideally the tracer must be eliminated rapidly from sites where there is no target molecule and from blood, so that a high contrast can be obtained between tumour and surrounding tissue.

History

PET has come a long way since researchers started working on the concept, due to the necessity of developing several elements that merged into the imaging modality we know today[1]. In the late 1950s the first successful transaxial emission tomography was developed. Early systems gave poor results because of inadequate reconstruction methods. The advancement of PET progressed slowly until the development of advanced reconstruction techniques that accompanied the development of CT. The driving force behind the use of positron emitters centered on the availability of radionuclides, surprisingly discovered more than 60 years ago. ^{11}C preceded ^{14}C by several years but had experimental limitations because of a very short half-life (20 minutes). Interest was rekindled some 20 years later when it was appreciated that their short half-lives and body-penetrating photons had potential to image biochemical transformations. The successful synthesis of ^{18}F-FDG (fluorodeoxglucose, a glucose analogue) by Wolf *et al* in the mid-1970s[2] and works in imaging glycolysis by Sokoloff *et al* in 1977[3] provided another impetus for PET development. Once the broad utility of this tracer was demonstrated, plus the concomitant creation of scanners as we know them today by a team which included physicists Michel Ter-Pogossian and Michael Phelps (Washington University School of Medicine, 1975)[4], the medical community became excited by the possibilities and began to clamour for more clinical applications[1].

Radiotracer production and imaging

A cyclotron accelerates a beam of protons using high voltage electrodes and directs it towards the target nuclei, thereby incorporating an extra proton into them. This generates new radioactive isotopes with a neutron-to-proton ratio which by definition makes them energetically unstable. Isotopes are then coupled to the compound of interest, which will allow the incorporation of the radiotracer into the cellular-physiological processes of interest. To become stable, the radioactive part of the tracer will undergo a process of decay whereby the excess proton is usually converted into a positron, a neutron and a neutrino. The positron travels up to a range of a few millimetres in body tissue before 'colliding' with an electron along its path.

continues on page 6

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Presentation: Rasilez® film-coated tablets containing 150mg and 300mg of aliskiren. **Indications:** Treatment of essential hypertension. **Dosage:** 150mg to 300mg once daily with a light meal, alone or in combination with other anti-hypertensive agents. No adjustment of initial dose required in elderly (>65 years), renal and liver impairment. Not recommended in patients under 18 years of age. **Contraindications:** ♦ Hypersensitivity to the active substance or excipients. ♦ Pregnancy. **Warnings/Precautions:** ♦ Increased risk of hyperkalaemia in patients receiving other RAS agents, and/or those with reduced kidney function and/or diabetes mellitus ♦ Caution in patients with heart failure ♦ Close medical supervision in patients with marked volume- and/or salt-depleted patients due to risk of hypotension) ♦ Caution in patients with severe renal dysfunction, renal artery stenosis, a history of dialysis, nephrotic syndrome, or renovascular hypertension ♦ Not recommended during pregnancy or when planning to become pregnant, to be discontinued if pregnancy occurs. ♦ Not recommended in breastfeeding women. ♦ In event of severe and persistent diarrhea, Rasilez® should be stopped. **Interactions:** ♦ Monitoring when used concomitantly with furosemide ♦ Interaction with ketoconazole ♦ Concomitant treatment with drugs that may increase serum potassium levels ♦ Possible interaction with digoxin, irbesartan, St. John's wort, and rifampicin ♦ Meals with high fat content substantially reduce absorption. **Adverse reactions:** ♦ Common: diarrhea ♦ Uncommon: Rash ♦ Rare: Angioedema. ♦ Laboratory values: decrease in haemoglobin and haematocrit, increase in serum potassium. Please refer to SmPC for a full list of adverse events. Legal Category: POM. **Pack sizes:** 28 film-coated tablets. Marketing Authorisation Holder: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. Marketing Authorisation Numbers: EU/1/07/405/001 - 020.
Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma, P.O. Box 124, Valletta, VLT 1000, Malta. Tel +356 22983217.

A practical and comprehensive overview of PET/CT – Part I

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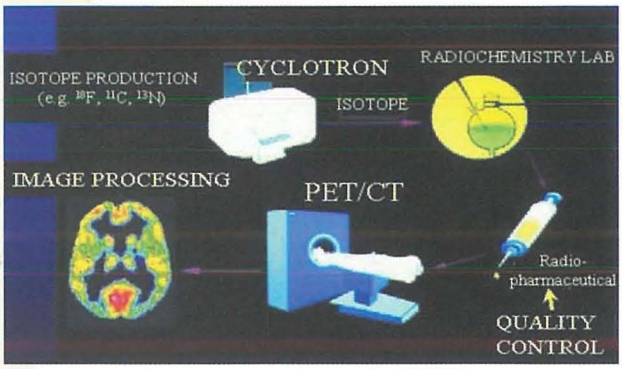

A summary of processes involved in PET/CT from tracer production to patient acquisition.

They together undergo an 'annihilation' process, producing energy in the form of two photons (gamma rays) of exactly equal energy (511 Kiloelectron Volts [KeV]), traveling in opposite directions (180 degrees of each other, starting from the same point). PET scanners contain several rings of hundreds of scintillation detector blocks (inorganic crystals) coupled to photomultiplier tubes. The pair of protons produced from a single annihilation will register simultaneously on opposing pairs of detectors as coincidence events. The paths of these two corresponding photons can thus be traced back (line of response). Detector rings register thousands of coincidence events emitted from the patient per second. For a coincidence event to be 'accepted' as correct, the photons must be registered within a very short time frame, otherwise it is discarded as a random event. Registered data is used to determine the source of positron annihilation at a given time. These data are then collected into 2D matrices (sinograms) which are then converted into tomographic 3D data using reconstruction software. PET/CT allows whole body imaging, hence imaging is not limited to any particular body district, especially in staging of oncology patients.

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Update on Avian Influenza

by **Tanya Melillo Fenech** *MD MSc*
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Department of Health Promotion and Disease Prevention

Study on environmental sampling during an Avian Outbreak in Cambodia

Samples were taken from the environment of households within one kilometre of the confirmed outbreak of birds or confirmed human cases. They sampled mud, still water (ponds), soil and water plants in and around 14 households areas in three villages with PCR testing. Viral RNA was detectable in poultry faeces, soil, some unconcentrated water, mud, water plants and feathers of dead poultry. However it was not possible to isolate any viruses so the role of environmental contaminants in infecting humans is so far still unclear. However it does reinforce the theory that those in contact with poultry and their detritus are at a potential risk of avian influenza and other zoonotic infections.

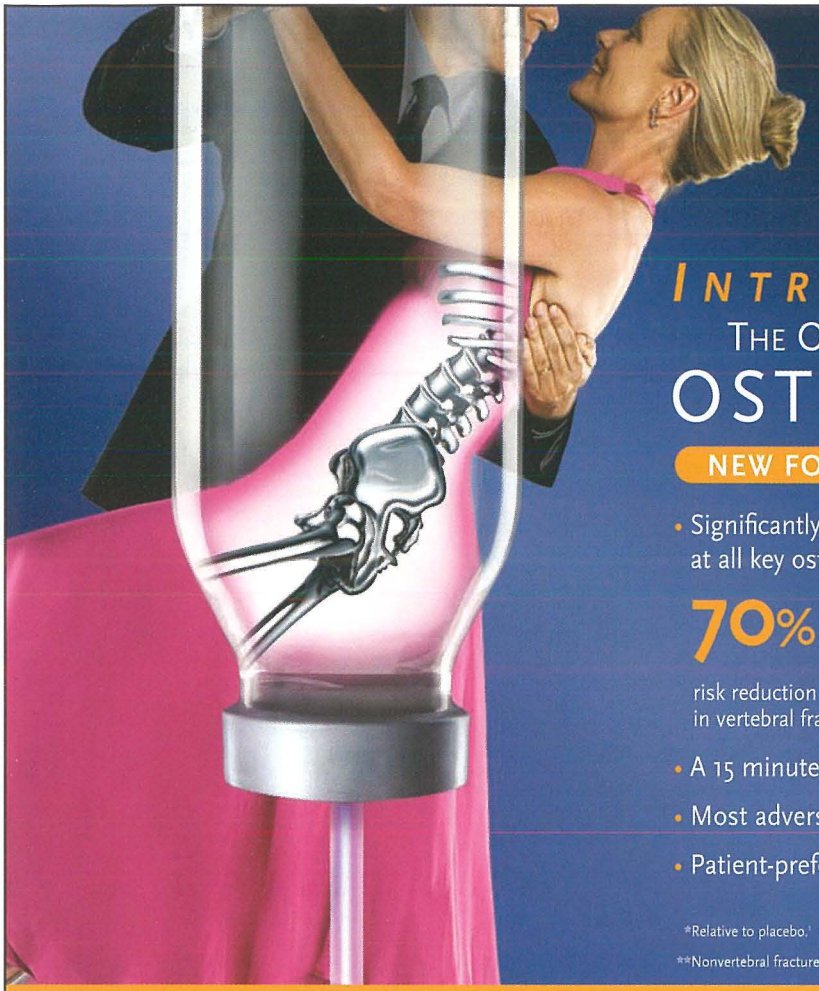
Update on Oseltamivir resistance in 2007-2008 seasonal influenza viruses in Europe

Although sporadic low level transmission of drug resistant viruses has taken place since 1999 when the Neuraminidase inhibitor drugs were first licensed, it was the winter season 07/08 that for the first time showed widespread and sustained transmission of such viruses in the community. Such viruses previously had not been able to readily transmit and had rapidly disappeared.

The proportion of Influenza A (H1N1) viruses that were found to be oseltamivir resistant varied significantly across Europe. The highest proportion of resistant viruses to date has been in Norway followed by Belgium, France, Netherlands and Luxembourg. Surveillance in previous years by the Virgil Project found <1% of circulating viruses to be resistant. There is no evidence that the appearance of these new viruses are related to use of oseltamivir which is currently not widely prescribed in most European countries. The European Centre of Disease Prevention and Control (ECDC) is now working with the manufacturer and national authorities to gather more information on routine oseltamivir use in Europe.

The clinical experience in Norway and elsewhere suggests that people who become ill with an oseltamivir resistant strain of Influenza A (H1N1) had a similar spectrum of illness to those infected with 'normal' seasonal influenza A, which can cause severe disease or death in vulnerable people (older people, those with debilitating illnesses and the very young).

At this stage the significance of these findings remains uncertain. The emergence of drug resistance in the context of limited drug use is unexpected, and the extent of future circulation is difficult to predict. The ECDC, WHO, European Influenza Surveillance Scheme (EISS), European Surveillance Network for Vigilance against Viral Resistance (VIRGIL) and authorities in the member states are undertaking intensive surveillance to monitor this.



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- 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 Solution for Infusion

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 at increased risk of fracture. Treatment of Paget's disease of the bone.

DOSAGE AND ADMINISTRATION: Post-menopausal Osteoporosis: A single intravenous infusion of 5 mg Aclasta administered once a year. 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. Not recommended for use in patients with severe renal impairment (creatinine clearance <40 ml/min). No dose adjustment in patients with creatinine clearance ≥40 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 <40 ml/min. Appropriate hydration prior to treatment, especially in the elderly and in combination with diuretics. Use with caution in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration), Pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly advised that patients with Paget's disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget´s disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. A patient being treated with Zometa should not be treated with Aclasta. As a precaution against osteonecrosis of the jaw (ONJ) a dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

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

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, diarrhoea, 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.

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ACL Ad1 09/08 MT

Peripheral arterial disease – a terrible misnomer

by **Kevin Cassar** *MD(Malta) MMEd(Dundee) FRCS(Edin) MD(Aberdeen) FRCS(Intercoll)*
Consultant Vascular Surgeon, Mater Dei Hospital

Peripheral arterial disease (PAD) has for far too long been treated as a minor 'peripheral' condition. The truth of the matter is that 'peripheral' arterial disease is associated with a three to four fold increased mortality compared to the general population. PAD is also associated with significantly increased morbidity from cardiovascular events such as myocardial infarction, cerebrovascular accidents and limb loss. Failure to recognise and treat risk factors in this group of patients results in preventable and unnecessary deaths, myocardial infarctions and strokes.

Peripheral arterial disease (PAD) is cursed by its own name. The Oxford English Dictionary gives the meaning of the word 'peripheral' as "irrelevant, marginal, nonessential and unimportant". Nothing could be further from the truth. PAD is only one manifestation of atherosclerosis, a systemic inflammatory condition affecting the coronary, cerebral and peripheral arteries. It is disease in the coronary and cerebral arterial beds that leads to the high mortality as well as the significant number of vascular events in this group of patients. There is abundant evidence to show that control of the major risk factors (hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking) and the administration of antiplatelet drugs can significantly reduce morbidity and mortality. Several national and international guidelines have been published to encourage adequate control of risk factors in an attempt to prevent deaths and vascular events. Despite these efforts, control of risk factors in this group of patients is often well below acceptable levels.

Peripheral arterial disease: just one manifestation of atherosclerosis

PAD, coronary artery disease and cerebral artery disease are all manifestations of the same systemic condition, atherosclerosis and it is therefore not surprising that the three conditions often affect the same patient. It is estimated that 65% of patients with PAD have coronary artery disease and/or cerebral artery disease.[1] In the primary care setting, 50% of patients with PAD are found to have coronary artery disease or cerebral artery disease. In patients with PAD referred to hospital, the prevalence of coronary artery disease is even higher. Furthermore the extent of coronary artery disease increases with the severity of peripheral arterial disease as estimated by ankle brachial pressure index (ABPI).[2] 50% of patients with intermittent claudication are also found to have significant carotid disease on duplex ultrasonography.[2]

Prevalence and Incidence of PAD in Malta

PAD may be completely asymptomatic, may present with intermittent claudication of the calves, thighs and or buttocks, or in its most severe form may result in critical ischaemia defined as either ischaemic rest pain or ischaemic tissue loss (ulcers or gangrene).

PAD is a common condition. No epidemiological studies have been carried out in Malta to identify the prevalence of PAD. The overall annual incidence of intermittent claudication is estimated to be between 4.1-12.9 per 1000 in men and 3.3-8.2 per 1000 in women.[3] Extrapolating this to our own population, we would expect an annual incidence of between 1333 and 5212 new patients with intermittent claudication based on a population of 404,039 (Census 2005 figures). Compare this to the incidence of all cancers (except squamous cell and basal cell carcinoma) reported for 2003 in Malta which was 659 (National Cancer Registry 2005).

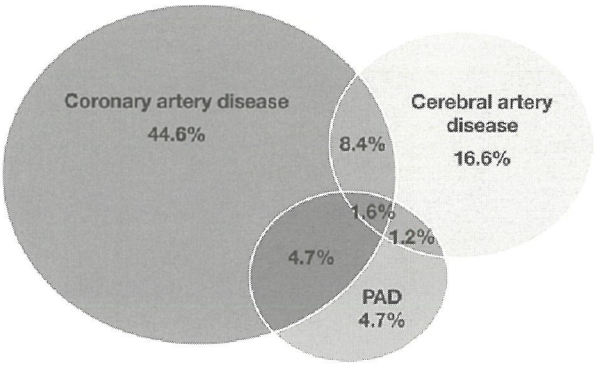

Figure 1: *Degree of overlap between the three conditions (Source: Norgren L, Hyatt WR, Dormandy JA et al. Intersociety consensus on the management of peripheral arterial disease)*

The prevalence of PAD, based on an ABPI <0.9, ranges from 139-169 per 1000 in men and 114-205 per 1000 women over 55 years of age.[4,5] Based on Census 2005 figures, the prevalence of PAD in Malta would be estimated to be between 15,652 and 28,147. These are huge numbers considering the size of our country and the resources available. Furthermore in view of the high prevalence of diabetes mellitus in Malta, it is likely that the true prevalence of PAD is likely to be towards the upper end of this estimate.

Morbidity and Mortality associated with PAD

The worse the severity of PAD as estimated by ABPI, the higher the risk of cardiovascular events and mortality. Death in this group of patients is overwhelmingly due to cardiovascular events with coronary artery disease accounting for 40-60%, cerebral artery disease for 10-20%, and ruptured abdominal aortic aneurysm accounting for another 10% of deaths.

In patients who have asymptomatic PAD or have intermittent claudication, the mildest form of the condition, the annual incidence of major cardiovascular events is between 5 and 7%.[2] Taking the lowest estimate of PAD prevalence and assuming that all patients with PAD in Malta have the mildest form of disease, this would amount to around 1100 major cardiovascular events per year.

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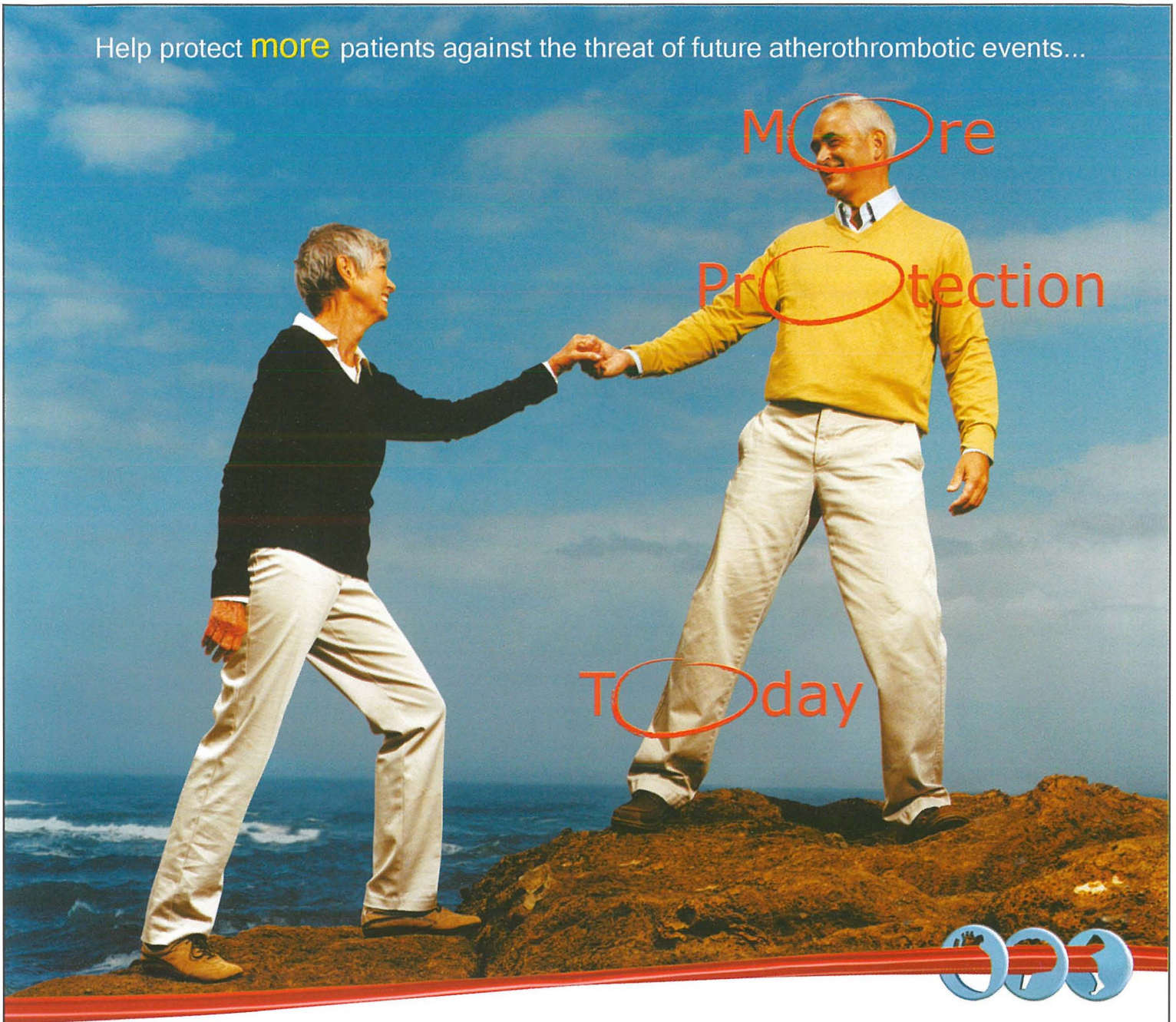

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NAME OF MEDICINAL PRODUCT: Plavix 75 mg film-coated tablets. COMPOSITION: Clopidogrel hydrogen sulphate 97.875mg. PHARMACEUTICAL FORM Film-coated tablet. THERAPEUTIC INDICATIONS Clopidogrel is indicated for the prevention of atherothrombotic events in: Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. Patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) in combination with acetylsalicylic acid (ASA). POSOLOGY AND METHOD OF ADMINISTRATION Adults and elderly: single daily dose of 75 mg with or without food. In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q wave myocardial infarction): single 300 mg loading dose and then continued at 75 mg once a day (with ASA 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months. Children and adolescents: There is no experience in children. CONTRAINDICATIONS Hypersensitivity to the active substance or to any of the excipients of the medicinal product; Severe liver impairment; Active pathological bleeding such as peptic ulcer or intracranial haemorrhage; Breast-feeding. SPECIAL WARNINGS AND PRECAUTIONS FOR USE Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, nonsteroidal anti-inflammatory drugs, heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings. If a patient is to undergo elective surgery and antiplatelet effect is not necessary, clopidogrel should be discontinued 7 days prior to surgery. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken. Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis. In view of the lack of data, in patients with acute myocardial infarction with ST-segment elevation, clopidogrel therapy should not be initiated within the first few days following myocardial infarction. In view of the lack of data, clopidogrel cannot be recommended in acute ischaemic stroke (less than 7 days). Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients. Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine. INTERACTION WITH OTHER MEDICINAL PRODUCTS: Warfarin; glycoprotein IIb/IIIa inhibitors; Acetylsalicylic acid (ASA); Heparin; Thrombolytics; Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Other concomitant therapy: No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. PREGNANCY AND LACTATION Pregnancy: As no clinical data on exposed pregnancies are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure. Lactation: It is not known whether this medicinal product is excreted in human milk. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Clopidogrel has no or negligible influence on the ability to drive and use machines. UNDESIRABLE EFFECTS: Haemorrhagic disorders; Haematological disorders; Central and peripheral nervous system disorders: Headache, Dizziness, Paraesthesia and Vertigo: Gastrointestinal system disorders: Diarrhoea, Abdominal pain, Dyspepsia, Gastric ulcer and Duodenal ulcer, Gastritis, Vomiting, Nausea, Constipation, Flatulence. Platelet, bleeding and clotting disorders; Bleeding time increased and Platelets decreased. Skin and appendages disorder: Rash and Pruritus. White cell and RES disorders: Leucopenia, Neutrophils decreased and Eosinophilia. Bleeding: some cases were reported with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage); skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding (conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), haematuria and haemorrhage of operative wound have been reported. Blood and lymphatic system disorders: Thrombotic Thrombocytopenic Purpura (TTP), severe Thrombocytopenia (platelet count ≤30 x109/l), Agranulocytosis, Granulocytopenia, Aplastic anaemia/Pancytopenia, Anaemia. Immune system disorders: Anaphylactoid reactions, Serum sickness. Psychiatric disorders: Confusion, Hallucinations. Nervous system disorders: Taste disturbances. Vascular disorders: Vasculitis, Hypotension. Respiratory, thoracic and mediastinal disorders: Bronchospasm, Interstitial pneumonitis. Gastrointestinal disorders: Pancreatitis, Colitis (including ulcerative or lymphocytic colitis), Stomatitis. Hepatobiliary disorders: Acute liver failure, Hepatitis. Skin and subcutaneous tissue disorders: Angioedema, Bullous dermatitis (erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis), Rash erythematous, Urticaria, Eczema and Lichen planus. Musculoskeletal, connective tissue and bone disorders: Arthralgia, Arthritis, Myalgia. Renal and urinary disorders: Glomerulonephritis. General disorders and administration site conditions: Fever. Investigations: Abnormal liver function test, Blood creatinine increase. OVERDOSE: No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel. MARKETING AUTHORISATION HOLDER: Sanofi Pharma Bristol-Myers Squibb SNC, 174 Avenue de France, F-75013 Paris – France. MARKETING AUTHORISATION NUMBER: EU/1/98/069/001a. FURTHER INFORMATION IS AVAILABLE FROM: sanofi-aventis Malta Ltd. Tel: 2149 3022

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Peripheral arterial disease – a terrible

continued from page 8

The outcomes in patients with critical limb ischaemia, the most severe end of the spectrum of PAD, are significantly worse. Patients with critical limb ischaemia have a mortality rate of 20% in the first year after presentation. Figure 2 summarises the results of several studies on mortality rates in patients with intermittent claudication and critical ischaemia compared to healthy controls. The striking point is that the 5 year mortality in patients with critical limb ischaemia is over 50%, worse than breast, colorectal or uterine cancer and similar to mortality from ovarian cancer (based on mortality data from the National Cancer Registry 2005).

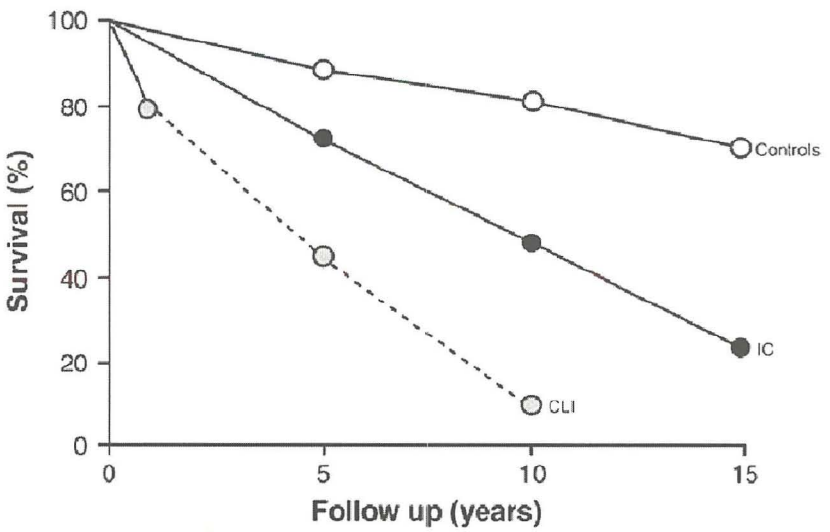

Figure 2: *Survival rate for controls, IC (Intermittent claudication) and CLI (critical limb ischaemia)*
(Source: Norgren L, Hyatt WR, Dormandy JA et al. Intersociety consensus on the management of peripheral arterial disease)

Control risk factors and save lives

Controlling risk factors significantly reduces the high rate of morbidity and mortality in PAD. Current international guidelines[2,6] recommend that all peripheral arterial disease patients should:

- Be prescribed an antiplatelet drug;
- Be prescribed a statin (unless their total serum cholesterol is below 3.5mmol/L);
- Stop smoking and be given help with smoking cessation (nicotine replacement treatment, bupropion, advice);
- Have their blood pressure controlled to less than 140/90mmHg or in diabetics or patients with renal insufficiency to less than 130/80mmHg;
- Have their blood glucose strictly controlled to achieve an HbA1c as close to 6% as possible if diabetic.

The use of antiplatelet drugs significantly reduces non-fatal myocardial infarction, non-fatal stroke and vascular death by a staggering 20%.[7] Based on estimates of prevalence of PAD in Malta, prescribing antiplatelet drugs to all PAD patients would prevent between 253 and 456 vascular events (non-fatal MI, non-fatal stroke and vascular death) each year. The first line treatment should be 75mg Aspirin because of its low cost. The CAPRIE study however showed that 75mg clopidogrel daily is significantly more effective than aspirin at reducing myocardial infarction, stroke and death (relative risk reduction 24% compared to aspirin).[8] In those who have contraindications to use of aspirin, clopidogrel is clearly an even more effective if somewhat more expensive treatment.

The Heart Protection Study showed that even patients with 'normal' cholesterol levels had a marked benefit from statin use.[9] Indeed the use of statins is associated with a 12% relative risk reduction in overall mortality, 17% reduction in vascular mortality, 24% reduction in coronary heart disease events, and a 27% reduction in all strokes over a five year period.[7] Extrapolating these figures to our local population, the use of statins would prevent between 281 and 506 deaths every five years. Furthermore it would prevent between 313 and 562 cardiovascular events in that same period, besides cutting the number of strokes and the number of patients requiring coronary or peripheral revascularisation. Considering all of this and the documented cost-effectiveness of these treatments it seems rather short-sighted to decline this group of patients free drug treatment, as is the case currently. Unfortunately despite the high morbidity and mortality associated with this condition, peripheral arterial disease does not feature on the "Schedule V" list of conditions and these patients are therefore not entitled to free medicines. In view of the cost of statins many of these patients cannot afford to purchase them.

How well are we doing at controlling risk factors?

We recently presented the data from an audit on risk factor management in peripheral arterial disease carried out at St Luke's Hospital.[10] Of all patients with PAD referred to a vascular surgeon, only 43% were on an antiplatelet drug, only 17% were on a statin and only 10% had been given any help with smoking cessation. This compares very poorly with a similar audit carried out in Scotland where 72% of patients were on antiplatelet treatment, 85% were on a statin and 85% had been given help with smoking cessation.[11] The major difference between these two countries is that all statins and antiplatelet drugs (including clopidogrel) are dispensed free of charge to Scottish patients and general practitioners are rewarded financially for achieving set targets.

The way forward

The prevalence of peripheral arterial disease will inevitably increase as the population grows older. It is high time that peripheral arterial disease sheds its 'Cinderella' status.

continues on page 24

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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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Presentation: Amlodipine and valsartan 5 mg/160 mg, 10 mg/160 mg film-coated tablets.
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Contraindications: Hypersensitivity to any component of Exforge or to dihydropyridine derivatives. 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 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 toghether with NSAIDs, COX-2 inhibitors, acetylsalicylic acid and non-selective NSAIDs. Concomitant 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, paraestesia. 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.
Packs and prices: Country specific.
Note: Before prescribing, please read full prescribing information.

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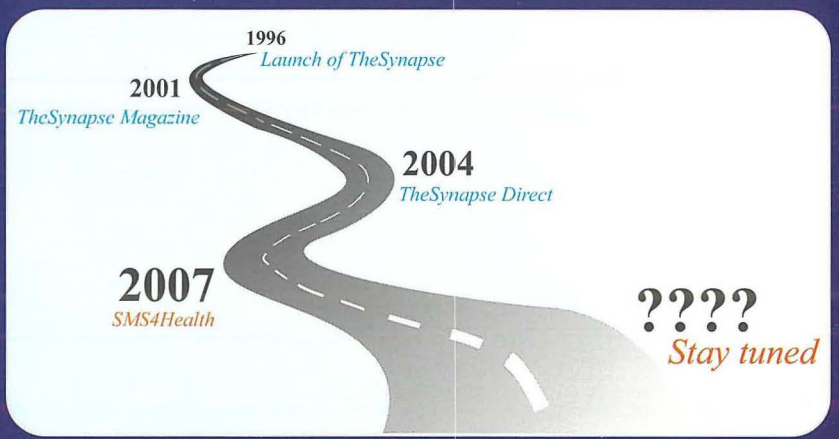
TheSynapse turns 12

by **Marika Azzopardi**

TheSynapse was launched on October 18, 1996. The original vision of Dr Wilfred Galea had always been to create a one-stop entry point for all members of the medical professions, providing them with all services to complement and facilitate their work, practically and literally at the tips of their fingers.

It is all a far cry from the simple bulletin board dial up system which could be made available to other professionals back in 1996. However, since the advent of the internet was in the pipeline it was decided to wait until the autumn to launch what would become 'The Synapse'. "I remember that back then, when I had approached people who could support the venture, with my idea of creating this internet portal, I had three distinctive categories of replies. One category commented with eagerness saying Good idea! I'm for it!' A second category told me, 'Wilfred, what is internet? Well, whatever it is, we have faith in what you're suggesting.' A final category just told me, 'Wilfred! Doctors don't use computers!' I assume the latter category have had time to re-think their words by now!"



Today, at a distance of 12 years, things have certainly moved steadily towards that direction and The Synapse is much more than a simple internet portal. In fact TheSynapse is now a suite of services which includes TheSynapse Internet portal and a range of other services under the same brand name. TheSynapse portal keeps members updated with relevant news from a number of reputable sources, both local and international. It is in fact an efficient service designed specifically for busy people.

The Synapse magazine was launched in 2001 and has gone a long way from the humble 4 page leaflet in black and white. The magazine is growing from strength to strength with regular contributions from leading specialists, newsworthy features and international medical news.

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Reversing Chronic Disease by Diet & Lifestyle Changes

An Introduction to Medicine of the Future – Available Today

by **Professor Albert Cilia-Vincenti** *MD FRCPath*

This is a brief introduction to future articles featuring the work of Dean Ornish, a Clinical Professor of Medicine and Founder President of the non-profit Preventive Medicine Research Institute at California University. Doctors and lay people often assume that medical advances are a new drug, a new laser, or surgery, which have to be high-tech and expensive in order to be effective. They often disbelieve that simple choices – what we eat, how we respond to stress, whether we smoke, how much we exercise, and the quality of our relationships – can make such a powerful difference to our health and survival.

Most publications on this subject are based on anecdotal evidence, the experience of others, or on wishful thinking, often making unfulfilled promises. Professor Ornish's work is unique, being based on 30 years research into what works, what doesn't, for whom, and under what circumstances. His recommendations are grounded in science, and have been proven to work:

- They help prevent, slow, stop, and even reverse progression of common deadly diseases, including coronary artery disease, prostate cancer, diabetes, hypertension, obesity, dyslipidaemia, arthritis, etc.
- His research team recently conducted the first study in men with prostate cancer showing that comprehensive lifestyle changes may change gene expression – turning on good parts of genes and turning off harmful ones.
- They recently conducted the first study showing how quickly comprehensive lifestyle changes may improve cellular age. *Telomeres* (DNA chromosomal ends) affect longevity. As they shorten and their structural integrity weakens, cells age, die quicker, and your life shortens.They found that *telomerase* (enzyme which repairs telomeres) increased significantly with their diet and lifestyle modification programme after only 3 months.
- Ornish's team has consistently shown that their programme can motivate many people to make and maintain bigger diet and lifestyle changes, and to achieve better clinical outcomes and larger cost savings than have ever been demonstrated.

The above is an outline of what Professor Ornish's research is about. Future articles will detail how and why the above claims work.

Professor Cilia-Vincenti is a former teacher of disease mechanisms in London and Malta Medical Schools, and has a special interest in natural medicine.

Health News

Bowel cancer - is it all in the genes?

Dr Lesley Walker

Director of Cancer information at Cancer Research UK

Scientists have identified new genes that can affect our risk of getting bowel cancer, according to new research published this week in Nature Genetics. Furthermore, one of the genes identified was shown to affect people differently, depending on their race.

The two studies are part of a series that are being funded by Cancer Research UK to search for bowel cancer susceptibility genes. The project aims to find a set of genetic markers that could be used to identify people in the population who are more at risk of bowel cancer.

In the first study, a team of scientists from the University of Edinburgh identified a genetic marker which was found to increase the risk of cancer of the colon (a type of bowel cancer) in Europeans, but not in people of Japanese descent. The second study identified two new genes that also appear to increase the risk of bowel cancer.

Director of cancer information at Cancer Research UK, Dr Lesley Walker, said "We can now begin to explain some of the difference in rates of the disease between populations through specific genes." She added, "This collaboration will continue to bring knowledge that will eventually allow us to test people with a family history of the disease, catching cancer earlier in those who are at the highest risk, or preventing it altogether."

However, it's important to remember that your risk of getting bowel cancer isn't just down to your genes - lifestyle factors also have an important role.

"Bowel cancer is not determined by genetics alone, and family history accounts for less than 10 percent of bowel cancer cases," commented Ian Beaumont, Director of Press, PR and Public Affairs at Bowel Cancer UK.

Philosophy of medicine – is there such a thing? – Part II

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

If medicine had no philosophy, no ethos, then there is nothing to stop us from making profit the main principle and from considering the motive factor as morally correct. This would be relativism at its best. Even if paradigms may be the rule of the day, it does not mean they are always correct (and many, including myself, do not believe in Big Bang, a term which after all was coined by its great opponent Fred Hoyle. Many are blind however and continue to work notwithstanding many unanswered questions). What results is that we try to build an ethics which suits our needs, as scientists would try to work around experiments which prove rather than disprove a theory.

This is perhaps the challenge of modern medicine today. We must not lose sight of what MacIntyre[1] calls the 'practice', which as a 'tradition' defines the goals and goods internal to the practice, even if the practice itself can have the benefits of 'external' goods, such as profits and prestige. The fact that we have to a certain extent omitted this has meant that defining and teaching of ethics within the medical community has been lost to external forces such as philosophy and sociology – all inputting, defining and dictating what doctors should or should not be doing. When the same people come on the hospital bed they will realise that they have been shouting in vain as they may indeed realise that the science of medicine is not, after all, the enemy. Then maybe, these much important fields will help medicine by becoming facilitative rather than didactive – that is, by helping the profession maintain its identity by their important contributions. Doctors will indeed appreciate the value of philosophy because they feel the need to *define* the philosophy of medicine. Medicine can only work within the cultural, social, and psychological spheres and does not concern itself, even if the rest of science does, with solely the scientific and biological. Perhaps that is why it continues to procure the title of an 'art' as well as a science. Yet it has to maintain a sense of what it stands for; even if assisted suicide may become acceptable to society, does this mean that doctors should do it?

Thus whereas Popper may have been wrong by strongly opposing what he called 'historicism', that is, the notion that historical instances made us into what we are today (one cannot argue that the second world war did not teach us lessons. One can forgive Popper for his ideas as he was an exiled Jew during the war, but what the 'historicist' philosophers such as Hegel really meant was that both good and bad work towards forming humanity, and not, that we are not free to choose our paths. He seemed to interpret Hegel as too deterministic on humanity and that thus the attempt at the extermination of the Jews was an inevitable process); Kuhn, on the other hand, with his notion of paradigms, puts us in dangerous grounds of having to define our ethos by the socio-psycho-cultural 'paradigm' of the day. This sets us back to having medicine defined by the regimes and thoughts of the day – as indeed was reflected in the Nuremberg trials.

If you have to be within a tradition to understand it and formulate your ethos with the changing times, then perhaps, Popper, with his limitations, gives us a better working formula, for at the end of the day medicine does move forward in research by 'challenges' to current thought, and when it comes to moral values and the goals of medicine, as MacIntyre said in his more analytical book *Whose Justice, Which Rationality?*[2], a tradition is upheld when it withstands the challenges of the times. This is why he upholds Aristotelian and Thomistic morality over the geneologists like Neitchze and Foucault who resent conservatism. Yet with its limits, conservative values have withstood challenges in time and indeed it is because of what was built on conservative values that the so-called post-modernist thought can build its nest. Yet at the same time conservatism has responded to changing times as well. If Christian values have withstood many tests in time, then one cannot blame medicine for upholding those values before it ventures too deep into research such as the New Genetics – for that would be the philosophy of this 'tradition'. To do this properly one has to give due importance to teaching young doctors the philosophy of their practice and tradition, which otherwise would simply be subject to relativist thoughts. One cannot then speak of a unifying tradition any longer.

If Christian values have withstood many tests in time, then one cannot blame medicine for upholding those values...

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Familial Mediterranean Fever – a common hereditary disease in Malta

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

Familial Mediterranean Fever (FMF), also known as recurrent polyserositis, is an autosomic recessive disease affecting the inflammatory pathway. Other related inherited conditions include hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) and the autosomal dominant Tumour Necrosis Factor Receptor-1-associated Periodic Syndrome (TRAPS). FMF is the most frequent of the group and as the name implies affects populations of the Mediterranean basin.

Though the disease is thought to be over 2000 years old, FMF was first identified as a distinct syndrome in 1945. Though it is considered to predominantly affect four populations (non-Ashkenazi Jews, Armenians, Turks and Arabs) it is also found in other populations of the Mediterranean.

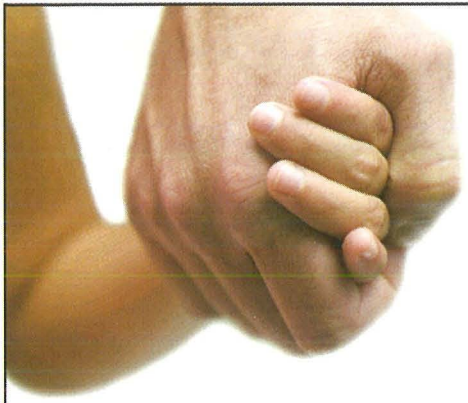
FMF is a disorder of inappropriate inflammation, where an event that under normal conditions can cause a mild inflammation, causes a severe response. The major pathophysiological characteristic of FMF is an inflammatory reaction of serosal tissues (pleura, peritoneum and synovium) with increased chemotactic activity of leucocytes, massive invasion of granulocytes of the affected tissues and fever. Typical precipitating factors include physical and emotional stress, a high-fat diet and menstruation. Though the causative mutations have been identified within the MEFV (Mediterranean Fever) gene, located on the short arm of chromosome 16, the exact function of the product of this gene (pyrin or marenostrin) is still unclear. This protein is involved in the regulation of apoptosis and inflammation through its regulation of caspase-1 activation and consequently, IL-1β production. This protein is basically expressed in granulocytes, in the serosal cells of the peritoneal and pleural spaces and in synovial cells. The recurrent inflammatory episodes are thought to produce excessive amounts of amyloid A protein that tend to deposit in the kidneys.

In around 50% of cases, the symptoms of FMF start during the first decade of life though a number of cases can be asymptomatic. The typical attack consists of fever lasting 1 to 4 days usually accompanied by serositis, with symptoms becoming less severe as the patient gets older.

continues on page 18

Typical attacks	**Fever** • 38–40°C, might be preceded by chills, lasting between 12 h and 3 days • Rarely the only manifestation of FMF
	Peritonitis • Clinically typical acute peritonitis, accompanied by either constipation or diarrhea (mostly in children). • Abdominal pain may persists for 1–2 days after the temperature returns to normal • May remain localised and simulate appendicitis or cholecystitis, less frequently mimicking renal colic or acute pelvic inflammatory disease • Up to 40% of patients may have undergone exploratory surgery with either appendicectomy or cholecystectomy
	Pleuritis • Frequent manifestation of FMF • In some cases an effusion can be identified at the costophrenic angle • May last as long as 7 days and be the presenting manifestation
	Pericarditis • Appears in a minority of patients and tends to be present at a late stage of the disease • Failure to distinguish pericarditis from pleuritis, might be the reason for the relative lack of identification of pericarditis
	Arthritis (typically hip, knee, ankle) • Common and important feature of FMF • There are three forms of arthritis which can be encountered: *Asymmetrical, non-destructive arthritis (75%)* - Short duration, with large effusions in one or two joints. Usually resolves completely *Chronic destructive arthritis (2–5%)* - hips and knees most commonly affected. Permanent damage may result *Migratory polyarthritis* - Similar to rheumatic fever and due to similar age of incidence misdiagnoses is a possibility
	Myalgia • Can be severe • Usually appearing in the arms and legs • May be associated with arthritis • Very rarely presenting as sole manifestation of FMF. Attacks may last more than 3 weeks
	Erysipelas-like skin lesion • Appears on the extensor surfaces of the leg, ankle joint or dorsum of the foot • Most commonly unilateral • Resembles erysipelas or cellulitis • Fades away spontaneously within 2-3 days
	Amyloidosis • Most severe complications of FMF • If affects the kidneys it results in renal insufficiency progressing to end-stage renal disease • May affect the gastrointestinal tract, liver, spleen, and at a later stage the heart and testes • Frequency of amyloidosis differs among the various populations and is arrested by colchicine use • Patients may present with renal amyloidosis but no history of typical FMF attacks
Incomplete attacks (with variation in severity and duration) involving 1 or more sites	**Characterised by recurrent abdominal pain and/or recurrent arthralgia (multiple, lower back, upper extremities)** Defined as painful and recurrent attacks that differ from typical attacks in 1 or 2 features, as follows: 1) the temperature is normal or lower than 38°C 2) the attacks are longer or shorter than specified (but not shorter than 6 hours or longer than a week) 3) no signs of peritonitis are recorded during the abdominal attacks 4) the abdominal attacks are localized 5) the arthritis is in joints other than those specified

Table 1 – *Typical features of Familial Mediterranean Fever*



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Other infections including septic abortion, puerperal sepsis and intra-abdominal sepsis. Section 5 gives a list of sensitive organisms. * Some members of these species of bacteria produce beta-lactamase rendering them resistant to amoxicillin alone. Infections caused by amoxicillin-susceptible organisms may be treated with NOPRILAM, due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms and beta-lactamase producers organisms sensible to amoxicillin/clavulanic acid association may be treated with NOPRILAM. Posology and method of administration. Adults- Mild to moderate infections: NOPRILAM 500 (500/125 mg), 1 tablet every 8 or every 12 hours. NOPRILAM DT (875/125 mg), 1 tablet every 12 hours. Severe infections (including urinary tract chronic or recurrent infections and lower respiratory tract infections). NOPRILAM 500 (500/125 mg), 1 to 2 tablets every 8 hours. NOPRILAM DT (875/125 mg), 1 tablet every 8 hours. CHILDREN- The dose shall be expressed according to the child's age and body weight, in mg/kg/day or in ml of suspension per dose. Children weighing 40 kg or over, use the adult's recommended dosage of the association amoxicillin/clavulanic acid. In children weighing less than 40 kg, other formulations than NOPRILAM DT (875/125 mg) should be preferred, according to the recommended dose (in mg/kg/day). Premature infants - No dose can be recommended for this age group. Children up to 12 years: Lower recommended doses (mg/kg/day): 25/3.6-45/6.4; Higher recommended doses (mg/kg/day): 45/6.4-70/10 The lowest dose is recommended for the treatment of skin and soft tissue infections and recurrent tonsillitis. The highest dose is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections. There are no clinical data available on the use of doses higher than 45/6.4 mg/kg/day (7:1 formulation) in children aged under 2 years. Contra-indications: NOPRILAM should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics, such as penicillins and cephalosporins. NOPRILAM is contra-indicated in patients with previous history of NOPRILAM-associated jaundice/hepatic dysfunction. Although NOPRILAM is generally well tolerated and has the low toxicity characteristic of the penicillin group of antibiotics, it is advisable to perform liver function, hematopoiesis and renal function tests periodically, if treatment is prolonged.Proper monitoring is thus recommended in patients on anti-coagulant therapy. NOPRILAM should be used with care in patients with evidence of hepatic dysfunction. Dosage should be adjusted in patients with renal impairment according to its severity. Oral suspensions with NOPRILAM contain aspartam and therefore shall be used with precaution in patients with phenylketonuria. 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Familial Mediterranean Fever – a common hereditary disease in Malta

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The frequency of attacks can vary between one every couple of weeks to one every 3-4 months, with the patient appearing completely normal in between attacks. The typical features of the disorder are listed in Table 1. Utilising these features one can arrive to the clinical suspicion of FMF by utlising a set of criteria, the most commonly used being the Tel Hashomer criteria (Table 2).[1]

The prevalence shows wide ethnic variation with a high prevalence amongst Armenian, non-Ashkenazi Jews, Levantine Arabic and Turkish groups with carrier frequencies of 1:7, 1:5, 1:5 and 1:5 respectively. Up to this date, over 80 disease-causing mutations have been identified in the MEFV gene. Most of the FMF cases are caused by four mutations within Exon 10 (M694V, V726A, M680I and M694I). The disease-causing role of another common mutation, E148Q, is still under discussion though there is a growing body of evidence that it is not a neutral polymorphism and as such it is recommended to consider it as a pathological mutation.

A preliminary analysis of the population frequency of the mutations that have been identified amongst Maltese patients (M694V, V726A and E148Q), has shown a carrier frequency of 1.6%, 2.2% and 6.4% respectively. From these data, the estimated carrier frequency amongst the Maltese population is of 1:17 (1:10 if one includes the E148Q mutation).

Major Criteria	Recurrent Fever Recurrent Peritonitis Recurrent Pleuritis Recurrent Pericarditis Recurrent Mono-arthritis Recurrent Erysipeloid erythema Mediterranean ancestry Positive family History
Minor Criteria	Incomplete abdominal attacks Incomplete chest attacks Incomplete joint attacks Exertional Leg pain Response to colchicine Recurrent Arthralgia Childhood onset Remissions during pregnancy Leukocytosis
Supportive Criteria	Family history of FMF Appropriate ethnic origin Age <20 years at disease onset Severe attacks, requiring bed rest Spontaneous remission Symptom-free interval Transient inflammatory response, with 1 or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen Episodic proteinuria/hematuria Unproductive laparotomy or removal of white appendix Consanguinity of parents
FMF Diagnosis: Requirements	Recurrent Fever with one of the following: ≥ 1 major criteria ≥ 2 minor criteria 1 minor criteria plus ≥5 supportive criteria 1 minor criteria plus ≥4 of the first 5 supportive criteria

Table 2 – *Criteria set for diagnosis of Familial Mediterranean Fever*[1]

All of the studies on the phenotype/genotype relationships done so far, have shown that the M694V allele is associated with a more severe form of disease, with an earlier age of onset, higher frequency of attacks and presence of arthritis, with (as expected) homozygotes showing a worse clinical picture when compared to compound heterozygotes with either the V726A, M680I and E148Q mutations and in those who carry these three mutations in any combination.

Considering that from the preliminary local results, FMF seems to be the most common single gene disorder on the Island and as this disorder has a high degree of morbidity and mortality and an effective (and relatively cheap) treatment is available, a population screening programme should be considered.

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TheSynapse turns 12

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Another important component of TheSynapse suite is TheSynapse Direct. "Many doctors include the facility of testing services within their practice. Instead of waiting for test results for days or having to collect them from independent laboratories, The Synapse Direct allows the doctor to securely download test results from his or her own clinic, directly onto the practice's record system. This makes for rapidity, ease of reference and a patient who can be seen to and reassured faster in the long run."

More innovations are in the pipeline. Dr Galea explains, "At this point we are looking at facilities that could help support a veritable community site for the medical profession. We would like to see more interaction between different members and spheres of the profession and, in our humble way, I believe we are succeeding in this regard. The Synapse today has close to 3000 members, including also international members."

Today Dr Wilfred Galea runs the whole system, backed by a team of people. "We've become a medical media company now. We are responsible for constantly updating material, keeping up with the continuous flow of information and newsfeeds. As regards information delivered, we believe that "if it's relevant, it's on TheSynapse"! And if it's something that can help interaction between colleagues, TheSynapse will definitely be adopting it along the way. I believe this is especially important in Malta's case since we are so very insular."

The Synapse - For further details contact *editor@thesynapse.net or search on http://www.thesynapse*.net

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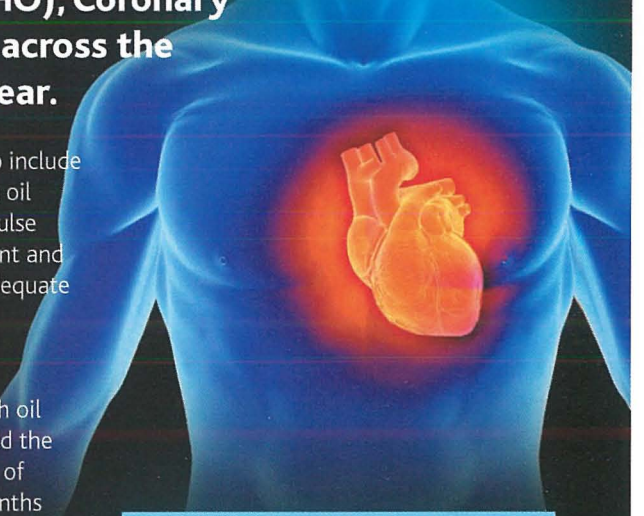

Factors affecting heart health

Many factors affect heart health, including getting older or family history, however, there are also things that can be done to improve the health of the heart, such as enjoying a healthy diet and active lifestyle which are both known to help keep the heart strong. In particular, research has shown that Omega-3 is an essential nutrient, which can help keep the heart healthy.

Omega-3 and the diet

Omega-3 fatty acids are a rich source of Essential Fatty Acids, EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). These polyunsaturated fatty acids are termed essential because the body needs them yet cannot produce them, therefore they must to obtained from the diet.

Clinical evidence is continuing to prove that Omega-3 nutrients play an important role in everyday health maintenance, however it is EPA, which plays a major role in heart health. EPA is converted by the body into prostaglandins, which contribute to the beneficial effects on the heart, helping to maintain a healthy blood flow.

Many people still find it difficult to include oily fish in their diet, therefore fish oil supplements such as Seven Seas Pulse Pure Fish Oils can offer a convenient and natural alternative to ensure an adequate level of Omega-3 is achieved.

Omega-3 and the heart

Omega-3 found in oily fish and fish oil supplements has been shown to aid the primary and secondary prevention of coronary heart disease. After 3 months of taking fish oil supplements patients surviving recent myocardial infarction significantly reduced their risk of death. Omega-3 Fatty Acids have been shown to protect heart health in a number of ways -

- By helping to keep blood vessels dilated
- By reducing high triglyceride levels
- By encouraging the development of a 'non-stick' lining to the arteries
- By inhibiting the inflammation of arterial plaques
- By maintaining arterial elasticity
- By lowering the blood pressure
- By improving circulation
- By helping to reduce homocysteine levels

Summary
Evidence links the consumption of Omega-3 to a reduction in the risk of developing coronary heart disease.

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The richest form of Omega-3 is found in oily fish. Expert bodies including the UK's Scientific Advisory Committee on Nutrition (SACN), whose advice was instrumental in forming the UK Food Standard Agency guidelines, recommend to the average person to increase their consumption of fish to two meals a week, one of which should be oily. These guidelines are scientifically well founded on a large body of evidence.

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Singing the Blues and The Beatles

by **Marika Azzopardi**

There is more to a histopathologist than meets the eye. And Dr James De Gaetano is an ideal example. Meeting him after a long day at the laboratory, he explains the ins and outs of his profession with enthusiasm.

"My work involves microscopic work on a diagnostic level. Basically I have to examine tissue extracted from patients after exploratory interventions and most of the times it heavily revolves around diagnosing cancer."

Dr De Gaetano admits the work is very difficult and intense, basically because it involves making highly responsible decisions around people's lives. "The cases I deal with are mostly paediatric which makes for an added responsibility. The work calls for determining decisions – Is the growth benign or malignant? How serious is this? How should it be handled? Any decision made by me will eventually reflect on the patient's life from then onwards. It can certainly bog you down. Having said that, however, I thoroughly enjoy it."

Not many doctors are interested in the field of histopathology and hence there are not many histopathologists around. Basically this could be traced down to the fact that most doctors look forward to patient contact which is non-existent in this speciality. One only gets to observe closely whatever is at the other end of the microscope and patients are only referred to as names. "That is something most doctors aren't too eager about. Moreover the work is particularly hard and requires several years of study. One needs a minimum of five years to specialise. Usually study is carried out partly in Malta and partly abroad, generally in the UK. In my case, I took up a fellowship in Australia."

Working constantly on the microscope can be very demanding, and Dr De Gaetano admits it can be pretty exhausting mentally. And so, to relieve the stress, he branched out into something completely different. In fact James De Gaetano is the leading vocalist in a band of (predominantly) doctors or medically-related professions – The Quacks.

With a name that parodies the medical profession, one can gauge that this can't really be serious business and is just an excuse for these professionals to let their hair down. But whatever the reason, the band has been going strong for the past decade or so and it was about two years old when Dr De Gaetano came to know of it. "It was nearly eight Christmases ago. We had been invited to a fundraising activity at St Luke's Hospital just before Christmas and The Quacks were playing. At the time the group was just doing instrumentals and playing 'Shadows' music mostly. I just walked up to the guitarists and asked if they needed a soloist."

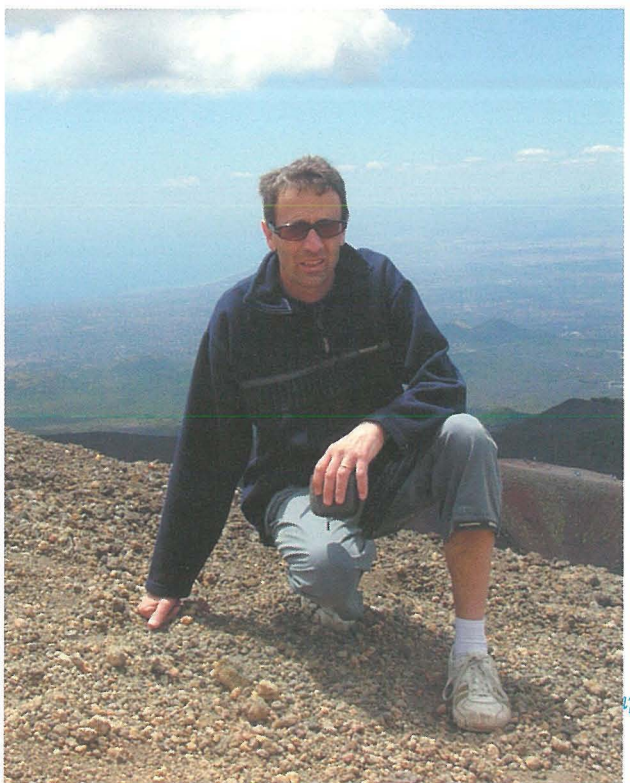
Drawing on his many years as a Voices component and his 1991 solo performance with this well-known choir, James De Gaetano felt it could be fun. And it all fell in place when he was contacted just two days later. The rest, as they say, is history.

Today the members of The Quacks whose ages span from the early 20s through to the late 50s, include himself as lead vocalist, Anthony Bernard (orthopaedic surgeon) as lead guitarist, Malcolm Crockford (radiologist) as rhythm guitarist, Mario Mifsud (radiographer) as bass guitarist, Adrian Curmi Dimech (a non-medical – "he doctors the accounts") as drummer, Antonella Bernard (another non-medical - Anthony Bernard's better half) as backing vocalist, and Nicky Farrugia (nurse) as backing vocalist.

The Quacks boast a specific genre of music – 60s and 70s songs and all the golden oldies courtesy of The Beatles, The Rolling Stones, The Monkeys and the like.

"We play strictly at fundraising events. We've done Caritas, Din l-Art Helwa, Hospice, Guh fl-Afrika and others. We did the August Moon Ball once but I guess that was the most formal event we've done so far and whilst we had to dress up to the nines, I'm not quite sure the invitees could actually waltz to our music. Most of the time, we just present ourselves in jeans and tees – it's that laid back and we do tend to start fooling around. And no, we don't get paid but we do get fed!"

Their individual busy schedules do not allow for more than a weekly rehearsal late on Sunday night accompanied by a bottle of good wine, and whilst they all enjoy a much awaited break during the summer, come autumn, their rehearsals resume with regularity with one extra practice night thrown in mid-week just before an event. "It takes time to build up a repertoire. At the moment we have about 50 songs in our repertoire plus some 10 'Shadows' instrumentals. Sometimes we think we'd like to have a pianist which would allow us a much wider portfolio. I know there are several doctors who are pretty good pianists. But so far we never recruited any."



Pancreatic

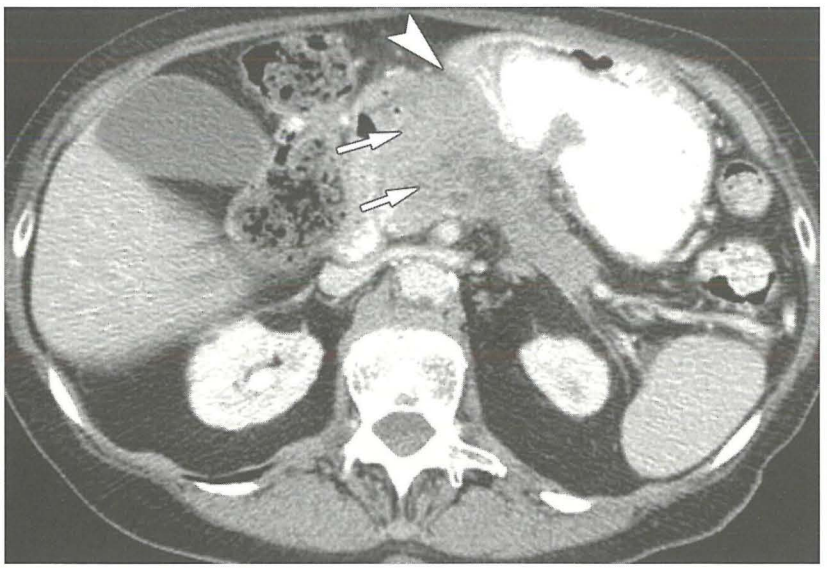


Figure 6. *Large exophytic mass (arrows) arising from the neck of the pancreas and invading the stomach (arrowhead), a finding that represents a radiologic T3 tumor.*

continued from page 2

T3 disease is defined as extension into the peripancreatic soft tissues, without invasion into the celiac axis or superior mesenteric artery (SMA) (figure 6), which invasion characterizes a T4 tumor (figure 7). Lymph node (figure 8) and extranodal (figures 9 & 10) metastases are well assessed by spiral CT.

Spiral CT is well suited for both tumor detection and assessment of resectability, but recently, endoscopic US also appears to be playing a complementary role in tumor assessment and lymph node staging, since it allows sampling of any suspect lymph nodes that are present. Comparative studies suggest that when preoperative staging is performed with both multidetector CT and endoscopic US, with one of the modalities being used for initial screening and the other in potentially resectable cases, the two modalities play complementary roles.

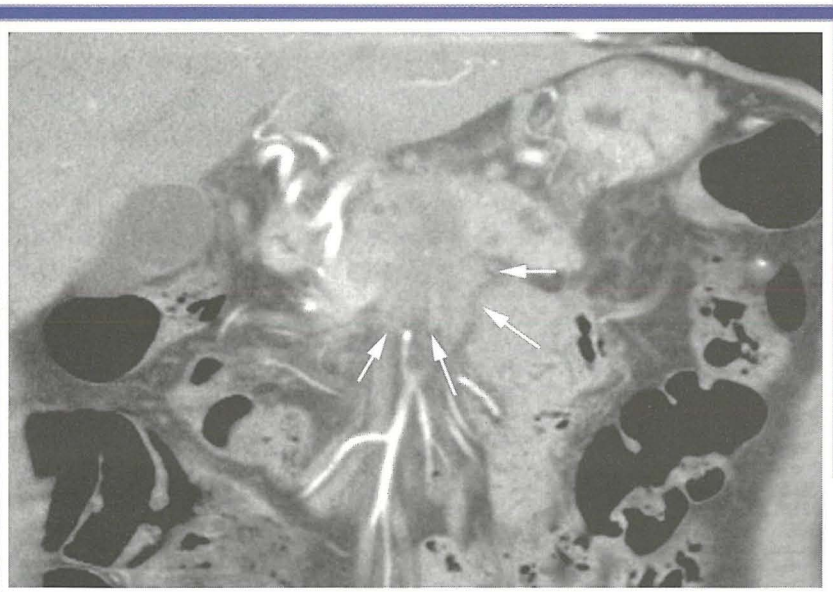


Figure 7. *Infiltration of mesenteric root (arrows) with encased branches of the enhancing SMA.*

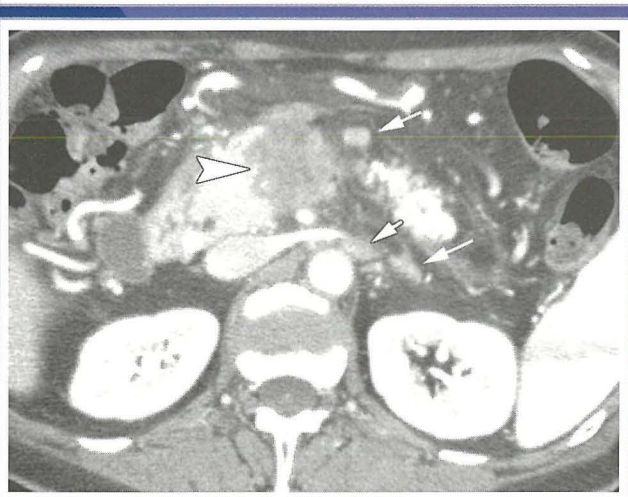


Figure 8. *CT scan shows a large pancreatic adenocarcinoma (arrowhead) as well as multiple surrounding peripancreatic lymph nodes (arrows).*

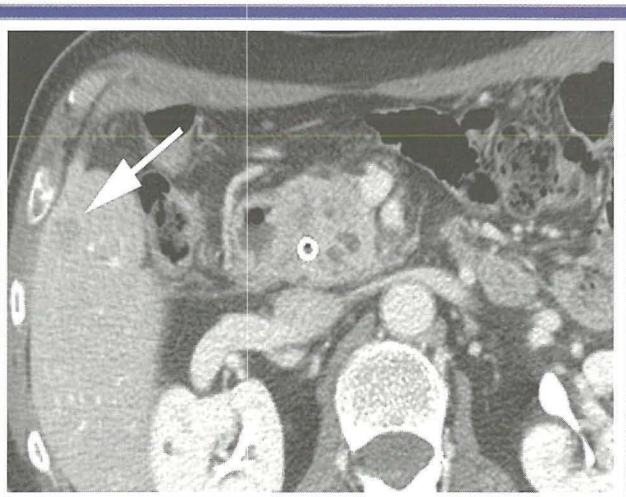


Figure 9. *Contrast-enhanced portal venous phase CT scan demonstrates a metastatic lesion in the liver (arrow).*

Cancer

Table 1: TNM Classification

Tumor Staging	
Tx	Tumor not assessed
Tis	Carcinoma in-situ
T1	Tumor < or = 2cm in diameter and confined to the pancreas
T2	Tumor >2cm in diameter and confined to the pancreas
T3	Tumor extends outside pancreas but does not involve celiac axis or SMA
T4	Tumor involves celiac axis or SMA
Lymph node Staging	
Nx	Lymph nodes not assessed
N0	Regional nodes not involved
N1	Regional nodes involved
Metastases (extranodal)	
Mx	Metastases not assessed
M0	No metastases
M1	Metastases present eg liver, lung, peritoneum

Table 2: Resectibility according to TNM stage

Stage 1	Resectible	T1 or T2, N0, M0
Stage 2	Usually Resectible	T1 or T2, N1, M0; T3, N0 or N1, M0
Stage 3	Unresectible	T4, N0 or N1, M0
Stage 4	Unresectible	T any, N any, M1

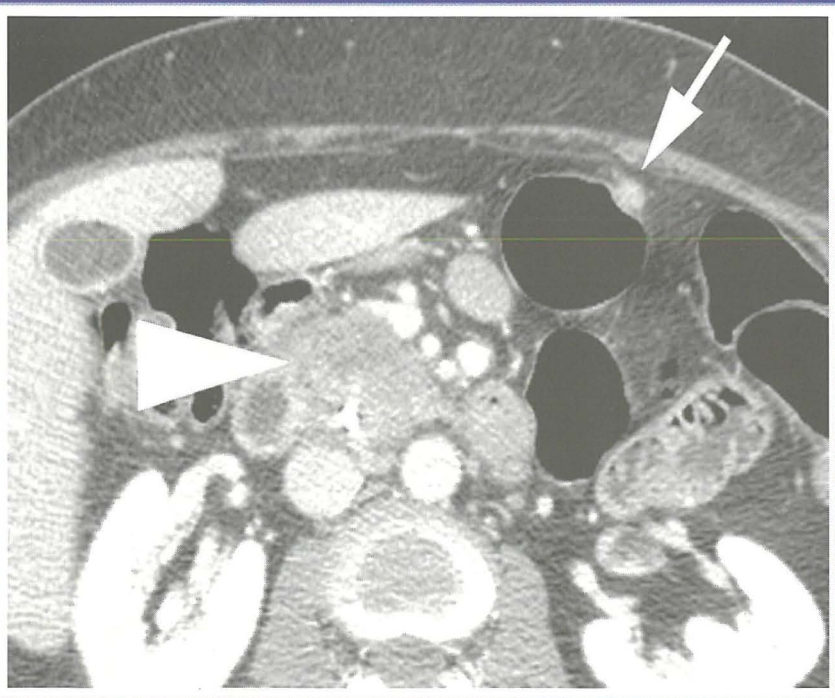


Figure 10. *Contrast-enhanced portal venous phase image shows a nodule on the inner surface of the peritoneum (arrow), consistent with peritoneal metastases. Arrowhead indicates the primary (pancreatic) tumor.*

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Peripheral arterial disease – a terrible misnomer

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As clinicians we need to recognise the fact that this is a 'killer' disease but more importantly that we can do something about it. Due pressure needs to be applied to the relevant health authorities to ensure that this group of patients are treated in the same way as patients with coronary heart disease with whom they share a common pathology, atherosclerosis, and equally high risks. Peripheral arterial disease patients deserve to be provided with the treatment required to reduce mortality and morbidity. Unless we act, we will continue to witness significant numbers of unnecessary and preventable deaths.

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