Issue 02/09

NEWSPAPER POST

TheSynapse

The Medical Professionals' Network

MEDICAL IMAGING

Fatty liver – What does this mean?

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

In the gastronomic sense, it would probably induce copious salivation and an urge for a thick slab of foie gras on toast and a glass of tannic red Bordeaux. But Hyperechoic liver texture compatible with fatty infiltration also happen to be frequent introductory statement on many of my abdominal ultrasound reports that are written at a time when I cannot afford such luxury. Fatty liver is a term applied to a wide spectrum of conditions characterized histologically by triglyceride accumulation within the cytoplasm of hepatocytes.

The two most common conditions associated with fatty liver are alcoholic liver disease and nonalcoholic fatty liver disease. Alcoholic liver disease is caused by excess alcohol consumption, whereas the nonalcoholic variant is related to insulin resistance and the metabolic syndrome. Other relatively common conditions associated with fat accumulation in the liver include viral hepatitis and the use or overuse of certain drugs. Rarer associated conditions include dietary and nutritional abnormalities and congenital disorders (Table 1).

These conditions all cause a triglyceride accumulation (steatosis) within hepatocytes by altering the hepatocellular lipid metabolism, in particular, by causing defects in free fatty acid metabolic pathways. Hepatocytes in the centre of the lobule (near the central vein) are particularly vulnerable to metabolic stress and tend to accumulate lipid earlier than those in the periphery. Consequently, in many of these conditions, steatosis tends to be most pronounced histologically in the zone around the central veins and less pronounced in zones around the portal triads. In advanced cases, there is diffuse, relatively homogeneous involvement of the entire lobule.

Most Common	Common	Rare	Congenital
Alcohol overuse	Viral infection	Nutritional or dietary abnormality	Monogenic disorders
Insulin resistance	Hepatitis C	Total parenteral nutrition	Metabolic disorders
Obesity	Hepatitis B	Rapid weight loss	Fatty oxidation defect
Hyperlipidemia	Drug use	Starvation	Organic aciduria
	Steroids	Surgery (eg, jejuno-ileal bypass)	Aminoacidopathy
	Chemotherapeutic agents	Iatrogenic injury	Storage disorders
	Amiodarone	Radiation therapy	Glycogen storage disorder
	Valproic acid		α_1-Antitrypsin deficiency
			Wilson disease
			Hemochromatosis
			Other
			Cystic fibrosis
			Dysmorphic syndromes associated with obesity
			Bardet-Bridel
			Prader-Willy

Table 1. Conditions associated with fatty liver disease.

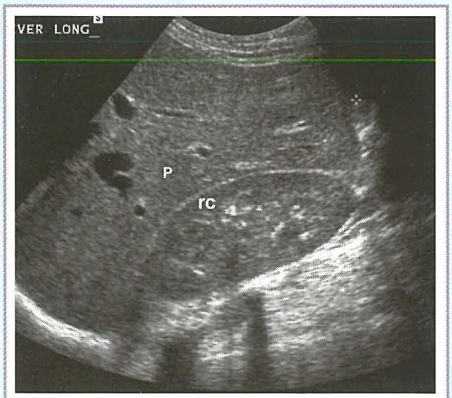


Figure 1. *Normal liver parenchyma (p) shows echogenicity similar to that of the adjacent right renal cortex (rc).*

In many conditions associated with fatty liver, steatosis may progress to steatohepatitis (with inflammation, cell injury, or fibrosis accompanying steatosis) and then cirrhosis. However, because progression to steatohepatitis is uncommon, a 'two-hit' model has been proposed. The 'first hit' is the cytoplasmic deposition of triglycerides in hepatocytes, which may make the hepatocytes more vulnerable to a 'second hit' but which, in the absence of the second hit, does not lead to progressive disease. The second hit has not yet been identified but is thought to represent a constellation of superimposed cellular events that promote inflammation and cell injury and incite progression to fibrosis and cirrhosis. In support of the two-hit model, there are data that suggest that the coexistence of steatosis with other liver diseases, such as viral hepatitis, increases the risk of disease progression.

The prevalence of fatty liver in the general population is about 15%, but it is higher among those who consume large quantities (>60 g per day) of alcohol (45%), those with hyperlipidemia (50%) or obesity (body mass index, >30 kg/m^2) (75%), and those with both obesity and high alcohol consumption (95%).

Common patterns include diffuse fat accumulation, diffuse fat accumulation with focal sparing, and focal fat accumulation in an otherwise normal liver. Unusual patterns that may cause diagnostic confusion by mimicking neoplastic, inflammatory, or vascular conditions include multinodular and perivascular accumulation. All of these patterns involve the heterogeneous or nonuniform distribution of fat.

On ultrasound, the echogenicity of the normal liver equals or minimally exceeds that of the renal cortex or spleen (Figure 1). Intrahepatic vessels are sharply demarcated, and posterior aspects of the liver are well depicted.

continues on page 20

Editor's Word

Bridge over troubled waters

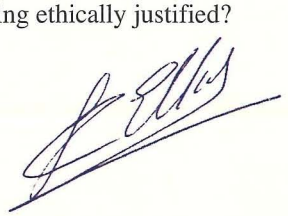
The credit crunch is in full sway, with some experts forecasting a year characterized by a global financial crises. Clearly demonstrating this, an important multinational generic company is being put up for sale, a deal which can reach $7.5 billion. On the other hand, this may provide a unique opportunity for brand-name pharmaceutical companies to diversify in the generic market, a strategy being followed by many to lengthen the profit life-cycle of drugs. We are also reading about Merck & Co's proposal to buy Schering-Plough for a mix of cash and shares valued at $41.1 billion, a deal which comes a few weeks after another US firm, Pfizer, announced its takeover of Wyeth for $68 billion.

This crisis may also be a golden opportunity for advertising campaigns of companies. According to research carried out on 600 US companies by McGraw-Hill between the 1980-1985 recession, if companies cut in their advertising budgets in an economic slump, the cost to regain market share once the economy turns round would cost much more than the cuts saved. However, on the other hand, according this research, companies which advertised aggressively during the recession had sales 256% higher than those who cut back on advertising.

Amidst all this, on a more positive note, in February, Finance Minister Tonio Fenech announced that a pharmaceutical company, Pharmacare Premium will be investing 10 million Euros on a new plant locally, which will be the first pharmaceutical company which will have a Maltese shareholding. Interestingly, it was reported that this investment will include research and development, something which this country sorely needs.

During the month of March, we have also seen US President Obama formally launch a drive for healthcare reform at a White House forum, telling experts about the costly and inefficient system which was dragging down the ailing US economy. In his budget plan, Obama has in fact allocated $634 billion to help pay for the overhaul over the next 10 years.

Also in March we have seen Obama lift restrictions on federal funding for human embryonic stem cell research, reversing restrictions placed on the research by his predecessor, George W. Bush, freeing labs across the country to start working with embryonic cells. This move, viewed by many as profit-driven, has placed stem cell research companies in a bull market. HOwever notwithstanding all this, ethical concerns have once again re-emerged – Can stem cell research instead be carried with adult stem cells or umbilical cord stem cells without the need to destroy embryos in the process? Is this funding ethically justified?



Contents

The Synapse Magazine
Issue 02/09

Published by Medical Portals Ltd
The Professional Services Centre
Guzi Cutajar Street
Dingli, Malta

Email: editor@thesynapse.net
Website: www.thesynapse.net

Editor:
Wilfred Galea

Scientific Editor:
Ian C Ellul

Administration Manager:
Carmen Cachia

Designer:
Conrad Bondin

ANNOUNCING GALVUS and EUCREAS
COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

GALVUS is a new DPP-4 inhibitor that improves glycemic control through powerful islet enhancement[1]

EUCREAS is the FIRST combination of a DPP-4 inhibitor, GALVUS, and metformin[2]

Galvus®
Presentation: Tablets containing 50mg vildagliptin. Indications: Treatment of type 2 diabetes mellitus as dual oral therapy in combination with: metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin; a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. Dosage: 100mg daily when used in dual combination with metformin or a thiazolidinedione administered as one dose of 50 mg given in the morning and one dose of 50mg in the evening. 50mg once daily in the morning when used in dual combination with a sulphonylurea. Vildagliptin may be taken with or without a meal. No dosage adjustment is required in the elderly, or in patients with mild renal impairment. Vildagliptin is not recommended in moderate to severe renal impairment or hepatic impairment including patients with pre-treatment ALT or AST >3xULN. Vildagliptin is not recommended for use in children and adolescents. Contra-indications: Hypersensitivity to the active substance or to any of the excipients. Precautions: Caution should be exercised in patients aged 75 years and older due to limited clinical experience. Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Due to limited experience, Vildagliptin is not recommended in patients with moderate to severe renal impairment or in patients with ESRD on haemodialysis. It is recommended that LFTs are monitored prior to initiation of Vildagliptin, 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 treatment 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. Due to limited clinical experience, use with caution in patients with congestive heart failure of NYHA functional class I II, and use is not recommended in patients with NYHA functional class III IV. In keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended. The tablets contain lactose; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Vildagliptin should not be used in pregnancy or lactation. 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. Side-effects: The majority of adverse reactions were mild and transient, not requiring treatment discontinuations. General: 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. Combination with metformin common: tremor, headache, dizziness, nausea, hypoglycaemia; uncommon: fatigue. Combination with a sulphonylurea common: tremor, headache, dizziness, asthenia, hypoglycaemia; uncommon: constipation; very rare: nasopharyngitis; Combination with a thiazolidinedione common: weight increase, peripheral oedema; uncommon: headache, asthenia, hypoglycaemia. Monotherapy dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory tract infection, arthralgia were reported in greater incidence than placebo; uncommon: hypoglycaemia. Legal Category: POM Packs: 28 tablets, Vildagliptin (Galvus®) 50mg tablets (EU/1/07/414/001-010). Marketing Authorisation Holder: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB.

Eucreas®
Presentation: Tablets containing 50mg vildagliptin and 850mg metformin or 50mg vildagliptin and 1000mg metformin. Indications: Type 2 diabetes mellitus in patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Dosage: Initiate at 50mg/850mg bd or 50mg/1000mg bd (morning and evening) based on patient's current dose of metformin. Dosing with or just after food may reduce gastrointestinal symptoms associated with metformin. There is no clinical experience of vildagliptin and metformin in triple combination with other antidiabetic agents. Vildagliptin/metformin tablets are not recommended in patients aged >75yrs or in patients <18yrs due to lack of data on safety and efficacy in these groups. Contra-indications: Hypersensitivity to the active substance or to any of the excipients; renal failure/dysfunction (CrCl <60 ml/min); acute conditions with potential to alter renal function (e.g. dehydration, severe infection, shock, i.v. administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (e.g. cardiac or respiratory failure, recent MI, shock); hepatic impairment, including patients with pre-treatment AST or ALT >3xULN; acute alcohol intoxication, alcoholism; lactation. Precautions: Vildagliptin/metformin tablets should not be used in patients with type 1 diabetes. Lactic acidosis (characterized by acidotic dyspnoea, abdominal pain, hypothermia, coma, decreased blood pH, plasma lactate levels >5mmol/l, increased anion gap and lactate/pyruvate ratio) can occur due to metformin accumulation (e.g. in significant renal failure, hepatic impairment). Other risk factors for lactic acidosis should be assessed (e.g. poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, conditions associated with hypoxia). If metabolic acidosis is suspected, treatment should be discontinued and the patient hospitalised immediately. Serum creatinine should be monitored at least once a year in patients with normal renal function and 2-4 times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients. Special caution should be exercised in elderly patients where renal function may become impaired (e.g. when initiating antihypertensives, diuretics or NSAIDs). It is recommended that LFTs are monitored prior to initiation of Vildagliptin/metformin tablets, at three-monthly intervals in the first year and periodically thereafter. If transaminase levels are increased, patients should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. If AST or ALT persist at 3xULN, vildagliptin/metformin tablets should be stopped. Patients who develop jaundice or other signs of liver dysfunction should discontinue vildagliptin. Following withdrawal of treatment with vildagliptin and LFT normalisation, treatment with vildagliptin should not be reinitiated. In keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended. Vildagliptin/metformin tablets should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards. Vildagliptin/metformin should be discontinued prior to, or at the time of, the administration of iodinated contrast agent and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal. Patients who experience dizziness as a side effect should avoid driving vehicles or using machines. Drug interactions: Vildagliptin has a low potential for interactions with co-administered medicinal products, including drugs that are substrates, inhibitors or inducers of CYP450 enzymes. In pharmacokinetic studies, no interactions were seen with pioglitazone, metformin, glibenclamide, digoxin, warfarin, amlodipine, ramipril, valsartan or simvastatin. As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) are co-administered. Glucocorticoids, beta-2-agonists, diuretics and ACE inhibitors may alter blood glucose. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of Vildagliptin/metformin tablets may need to be adjusted during concomitant therapy and on its discontinuation. Side-effects: The majority of adverse reactions were mild and transient, not requiring treatment discontinuations. General (vildagliptin): rare cases of hepatic dysfunction (including hepatitis). ALT or AST elevations ≥3xULN for vildagliptin 50mg od (0.2%), vildagliptin 50mg bd (0.3%) compared to 0.2% with comparators in clinical trials. Rare cases of angioedema at similar rates to controls. Vildagliptin and metformin in combination common: tremor, headache, dizziness, nausea, hypoglycaemia; uncommon: fatigue. Vildagliptin monotherapy sommen: dizziness; unsommen: 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.

NOVARTIS

Galvus® vildagliptin

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

Eucreas® vildagliptin/metformin

GAL Ad1 03/09 MT

The spirit of Alma-Ata

by **Francesco Carelli**

Thirty years ago, the Declaration of Alma-Ata defined health as a "complete physical, mental and social wellbeing and not merely the abssence of disease or infirmiy" and also stated that the access to basic health services was a fundamental human right.

What is the meaning of going back to Alma-Ata now? It leads to an enhancement of the provision of primary care because the challenge for medicine in the third millennium is to achieve the right balance between modern technologies and interpersonal relations. A shift was made, which is characteristic for Family Medicine, from patient to person, from treatment to care given in a network of relationships.

EURACT is stressing the Alma-Ata philosophy, promoting high levels of teaching and health promotion, and looking for mandatory specific training.

Doctors are involved in rational decisions, and during their undergraduate and vocational training they need to consider the interrelationships between health and social care, the impact of poverty, ethnicity, inequalities, and the structure of the health care system in which they live and in which they work[1].

Thirty years ago, the Declaration of Alma-Ata defined health as a "complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" and stated that the access to basic health services was a fundamental human right. The model adopted to provide healthcare services was "primary health care" (PHC). This means universal, community-based preventive and curative services, with a great community involvement. We could surely say that the definition of health as complete wellbeing is not realistic, but it is now time to rediscover the spirit of Alma-Ata, developed in 1978 in the Soviet Union, when the Cold War was still ongoing and when Internet was still unheard of.

It is worth remembering the context of the 1970s which faced policy-makers and general practitioners alike. The 1973 oil price crisis and the resulting 'new economic order' precipitated a series of social reforms including in the health sector, one of which was the International Conference on Primary Health Care in September 1978, in Alma Ata (the former capital of Kazakhstan and now known as Almaty). It was organised by the World Health Organisation and UNICEF and brought together 134 countries and 67 international organisations. The conference culminated in the issue of a declaration which defined and gave international recognition to the concept of PHC: the Alma-Ata Declaration.

Two really important documents have tried to make the Alma-Ata ideals a practical reality for patients. The WONCA Europe Definition has set out the range of skills required to practise the kind of primary health care envisaged in the Alma-Ata declaration. The EURACT Educational Agenda seeks to equip future generations of doctors in the same way.

continues on page 24

INTRODUCING ACLASTA®

THE ONCE-YEARLY INFUSION OF POWERFUL

OSTEOPROTECTION

NEW FOR POSTMENOPAUSAL OSTEOPOROSIS

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

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

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

*Relative to placebo.[1]

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

Aclasta® 5 mg

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

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

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

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

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

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

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

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

LEGAL CATEGORY: POM.

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

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

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

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

NOVARTIS

Aclasta®

zoledronic acid 5 mg solution for infusion

One Infusion. Yearlong Osteoprotection.

ACL Ad1 03/09 MT

Coeliac Disease – The Wandering Iceberg

by **Christian A Scerri** *MD PhD (Molecular Genetics)*
Consultant Geneticist
Mater Dei Hospital

Coeliac disease (CD), also known as coeliac sprue, non-tropical sprue, and gluten-sensitive enteropathy, is an inflammatory disease of the upper small intestine that results from gluten ingestion in genetically susceptible individuals[1].

The characteristic mucosal inflammation, villous atrophy and crypt hyperplasia that occur upon exposure to gluten leads to malabsorption of several important nutrients. CD was first formally described in 1888, by Samuel Gee in the St Bartholomew's Hospital reports[2]. The central role of gluten in the pathogenesis of CD was observed by Dicke in 1950[3]. He noted that persons previously diagnosed with CD improved during World War II when grain products were in short supply whilst when grains became more plentiful after the war, the incidence of coeliac disease returned to its pre-war levels. CD is associated with dermatitis herpetiformis[4] a typical skin rash that similarly to CD responds to withdrawal of gluten. Untreated CD is associated with multiple, short and long-term complications including nutritional derangements, anaemia, reduced bone density, as well as intestinal lymphoma.

Though its triggering factor (surgery, pregnancy, childbirth, viral infections and stress have all been implicated at some time or other) and its polygenic basis is still mostly unknown, CD is unique amongst the inflammatory diseases in that the causative agent is known, i.e. gluten. This fact projects CD as a possible model for the study of inflammatory disease.

In the 1980's, Marsh demonstrated that the immune system played an important role in causing intestinal injury in coeliac disease[5]. It has been shown that CD is the result of the activation of both a cell-mediated (T-cell) and humoral (B-cell) immune response upon exposure to the glutens (prolamins and glutenins) of wheat, barley, rye, and oats, in a genetically susceptible person[6].

CD was thought to be uncommon but in the last two decades, it has been realised that the condition is relatively common, affecting 1 in every 100 persons[7-9] to 1 in 50 persons[10]. Traditionally CD was regarded as a childhood disease but it is now clear that CD can occur at any age, with the fifth decade being the peak incidence in adults. Females are more commonly affected than males with a female to male ratio of around 3 to 1. The increased incidence of the condition can be partly explained through the greater awareness of its presentation and the availability of accurate serologic tests, though an actual increase as a result of as yet unknown triggering factors cannot be ruled out. The serological tests that helped to put CD in the forefront are the anti-gliadin antibodies (IgA and IgG), anti-endomyseal antibodies and recently the identification of anti-Transglutaminase antibody. The latter test has a very high sensitivity and specificity (99% and 98% respectively) making it ideal as an initial screening test.

Genetic predisposition, as indicated by the high concordance between monozygotic twins and the high prevalence amongst family members of affected individuals, plays a major role in CD. In the last decade or so considerable progress has been made in identifying genes that are responsible for CD predisposition. HLA Class II genes have been positively identified as a predisposing genetic factor for CD. The condition is strongly associated with the specific HLA class II genes known as HLA-DQ2 and HLA-DQ8 located on chromosome 6p21. HLA-DQ2 is found in the majority of CD patients (95%) whilst the remaining are usually HLA-DQ8 positive. As the HLA-DQ2 allele is very common in the population (around 30% of Caucasian individuals), it was clear that though the HLA type background is necessary for CD, it is not sufficient for CD to develop. The HLA locus has been assigned as the *CELIAC1* locus. HLA testing, specifically for the DQ2 and DQ8 alleles, is useful as an exclusive test, i.e. those individuals that are negative for the DQ2 and DQ8 are very unlikely to have CD.

Non-HLA genes have a higher genetic contribution towards CD compared to HLA genes; however, the predisposition depends on a number of genes, each of which adds a minor contribution to disease development. This small effect size compounded with genetic heterogeneity between populations, has made non-HLA coeliac disease predisposing genes very difficult to identify and reproduce.

The *CELIAC2* locus has been identified on chromosome 5, delimited by the genetic markers D5S410 and D5S402 within region 5q31-q33. This marker has been confirmed as a disease locus for CD in the recent European Cluster study on CD[11]. Though a number of inflammatory related genes exist in this area, the positive identification of the actual gene involved has remained very elusive.

The *CELIAC3*, corresponds to the CTLA4 region on chromosome 2. This region contains three genes, the CTLA4 gene, CD28 and ICOS, whose products are involved in the activation and control of the T-Cells. CTLA4 and CD28 cellular membrane proteins compete for the Antigen Presenting Cell (APC) membrane protein, CD80/86.

continues on page 8

FIRST NEW CLASS IN
10 YEARS!

A breakthrough in hypertension management:

RASILEZ®

The Direct Renin Inhibitor.

DRIVE

more complete Renin System control.[1]

Greater and extended BP efficacy[2-5]

- More complete control of the Renin System[1]
- Powerful BP reductions alone and in combination[2,5,6]
- Double-digit BP reductions beyond 24 hours[5]
- Placebo-like tolerability[2,5,6]

1. Azizi M, et al. J Am Soc Nephrol. 2004;15:3126-3133.
2. Uresin Y, et al. JRAAS 2007; 8(4):190-198.
3. Gradman, AH, et al. Circulation. 2005;111:1012-1018.
4. Schmieder RE, et al. Circulation 2009; 119:417-425.
5. Oh BH, et al. J Am Coll Cardiol. 2007;49:1157-1163.
6. Oparil S, et al. Lancet 2007; 370: 221-229.

NOVARTIS

Rasilez® aliskiren

DRI power that lasts.

RAS Ad1 03/09 MT

RASILEZ® BSS

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. Grapefruit juice should not be taken together with Rasilez®. **Contraindications:** • Hypersensitivity to the active substance or excipients. •Pregnancy .•Concomitant use with ciclosporin, quinidine and verapamil (highly potent P-gp inhibitors). **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 serious congestive 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.•Caution with moderate P-gp inhibitors such as ketoconazole. **Interactions:**•Monitoring when used concomitantly with furosemide • 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.•Concomitant treatment with P-gp potent inhibitors (eg. Ciclosporin).•Concomintant use with ketoconazole or other moderate pgp inhibitors (itraconazole, clarithromycin, erythromycin, amniodarone, telithromycin).•Caution with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other substances that may increase serum potassium levels.•Grapefruit juice. **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:** 7, 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. (vsn 2008-MT-Oct)

Coeliac Disease – The Wandering Iceberg

continued from page 6

If the latter product is missing, the T-cell undergoes apoptosis, whilst its interaction with CD28 induces T-cell proliferation and differentiation and its interaction with CTLA4, produces T-cell growth arrest. Thus, it was postulated that changes in the molecular structure of either of these two proteins could result in over-stimulation of the T-cell with the resultant intestinal damage typical of coeliac disease. In actual fact, single nucleotide polymorphisms (SNPs) within this group have been associated with the condition whilst in others, including the local coeliac population the same SNPs have been found to be protective.

CELIAC4 locus is located on chromosome 19p13.1. Studies on the *CELIAC4* locus revealed a significant and replicable association to a common variant located in intron 28 of the gene myosin IXB (MYO9B). A defect in MYO9B may be a factor involved in the early mucosal events preceding the inflammatory response. A genetic variant in the 3-prime part of MYO9B may interrupt the tight junction gate, consequently the immunogenic gluten peptides can enter the deeper mucosal layer more easily.

In addition to the above, a number of genes have been associated with CD, in most cases following the genome-wide association study. Locally studies have been undertaken utilising a genome-wide linkage analysis approach on large families with multiple affected members. Though this work is still in its infancy, a novel mutation on the gene encoding the CD44 and another mutation for the gene encoding the CD59 cell surface proteins were identified.

As a conclusion, it appears that the genetic predisposition to CD depends on a single gene with a large effect (HLA-DQ2/DQ8), with a large group of other genes affecting the various aspects of innate and adaptive immunity and intestinal permeability.

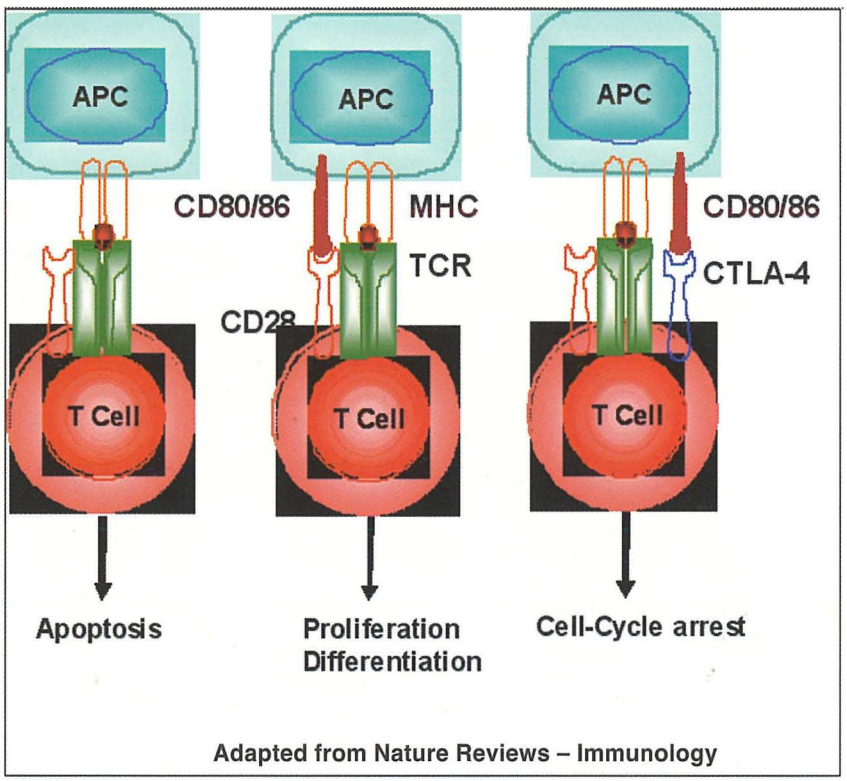
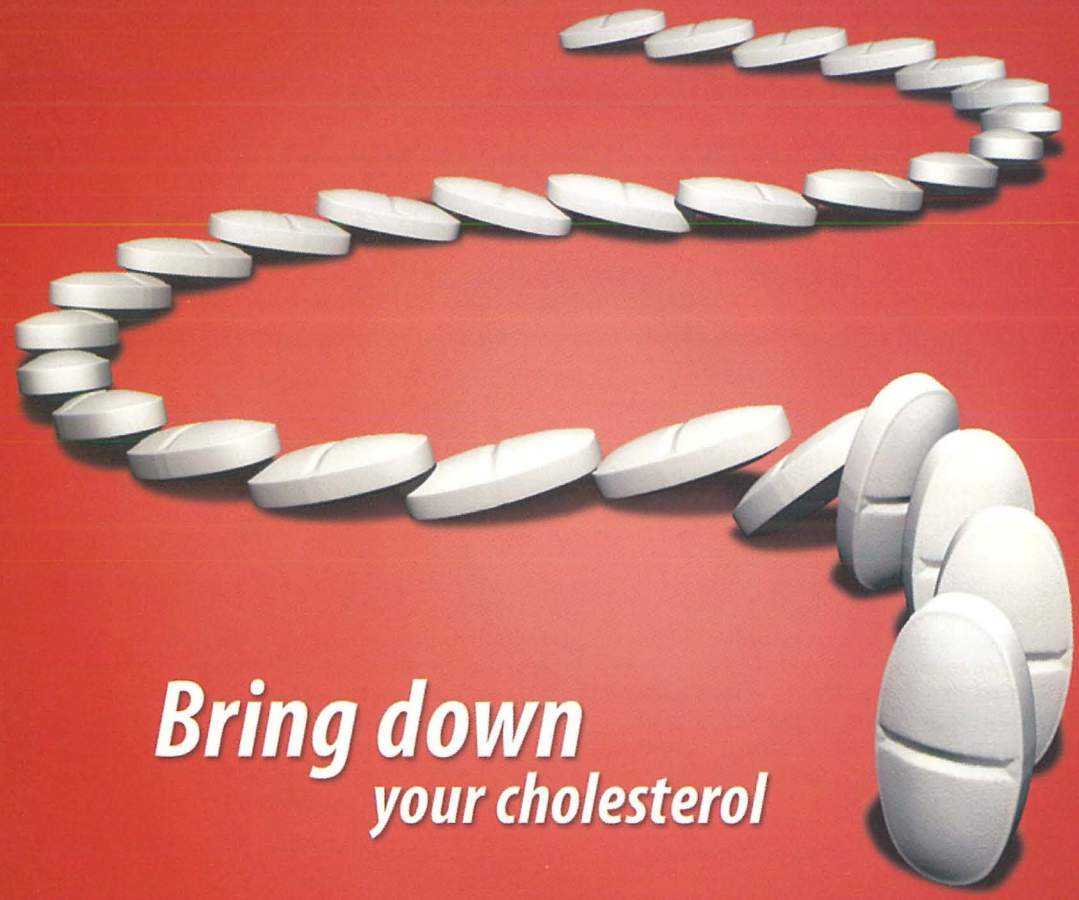


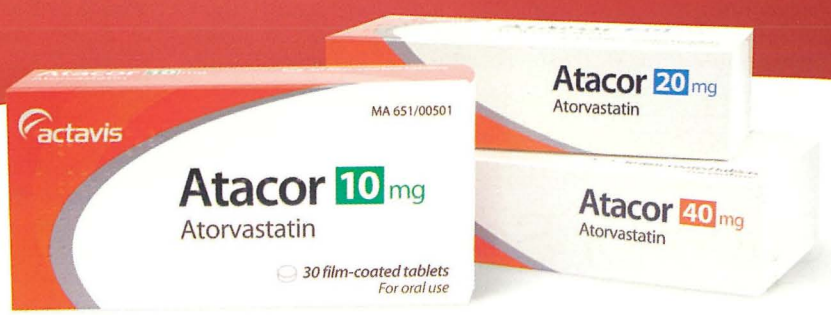
Figure1. *Interaction between the APC, T-cell, CD28, and CTLA-4.*

References

1. Cooke WT, Holmes GKT. Coeliac disease. Churchill Livingstone, London, 1984.
2. Gee S. On the coeliac affection. *St Bartholomew's Hospital Journal* 1988; 24:17–20.
3. Dicke WK. Coeliakie. PhD thesis. University of Utrecht: the Netherlands, 1950.
4. Shuster S, Watson AJ, Marks J. Coeliac syndrome in dermatitis herpetiformis. *Lancet* 1968; 1:1101-6.
5. Marsh MN. Studies of intestinal lymphoid tissue: the cytology and electron microscopy of gluten-sensitive enteropathy, with particular reference to its immunopathology. *Scandinavian Journal of Gastroenterology Supplement* 1981; 70:87-106.
6. Van de WY, Kooy Y, van Veelen P et al. Coeliac disease: it takes three to tango! *Gut 2000;* 46(5):734-7.
7. Grodzinsky E, Franzen L, Hed J, Strom M. High prevalence of celiac disease in healthy adults revealed by antigliadin antibodies. *Annals of Allergy* 1992; 69:66-70.
8. Fasano A. Where have all the American celiacs gone? *Acta Paediatr Suppl.* 1996; 412:20-4.
9. Catassi C, Fabiani E, Ratsch IM et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatrics* 1996; 412(Suppl):29-35.
10. Lohi S, Mustalahti K, Kaukinen K et al. Increasing prevalence of coeliac disease over time. *Alimentary Pharmacology & Therapeutics* 2009; 26(9):1217-25.
11. Babron MC, Nilsson S, Adamovic S et al. European Genetics Cluster on Coeliac Disease. (2003) Meta and pooled analysis of European coeliac disease data. *Eur J Hum Genet* 2003; 11(11):828-34.



Bring down
your cholesterol



Atacor

Atorvastatin

10mg, 20mg, 40mg tablets

Lipid Reducing Agent

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

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

This medicinal product is subject to a medical prescription.

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

actavis

creating value in pharmaceuticals

Professor Basant K. Puri's Medical School Talk – Part II
Fatty Acids, Depression, Schizophrenia & Huntington's Disease

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

Depression is claimed to be reaching epidemic proportions in the Western world, and many modern social factors have been blamed, such as job insecurity, isolation from family support, lack of religious belief, high divorce rate, stress from modern technology, pollution, the speed of modern life, and greater access to drugs and alcohol.

But alongside these social factors, depression is also thought to have a significant biological component, and so the main thrust of researching depression has been on neurotransmitters, such as serotonin and noradrenaline, and their mood-modifying effect. Low levels of neurotransmitters are strongly associated with depression, but have not been proved to be the cause of it, and play only one role among many in the depression story.

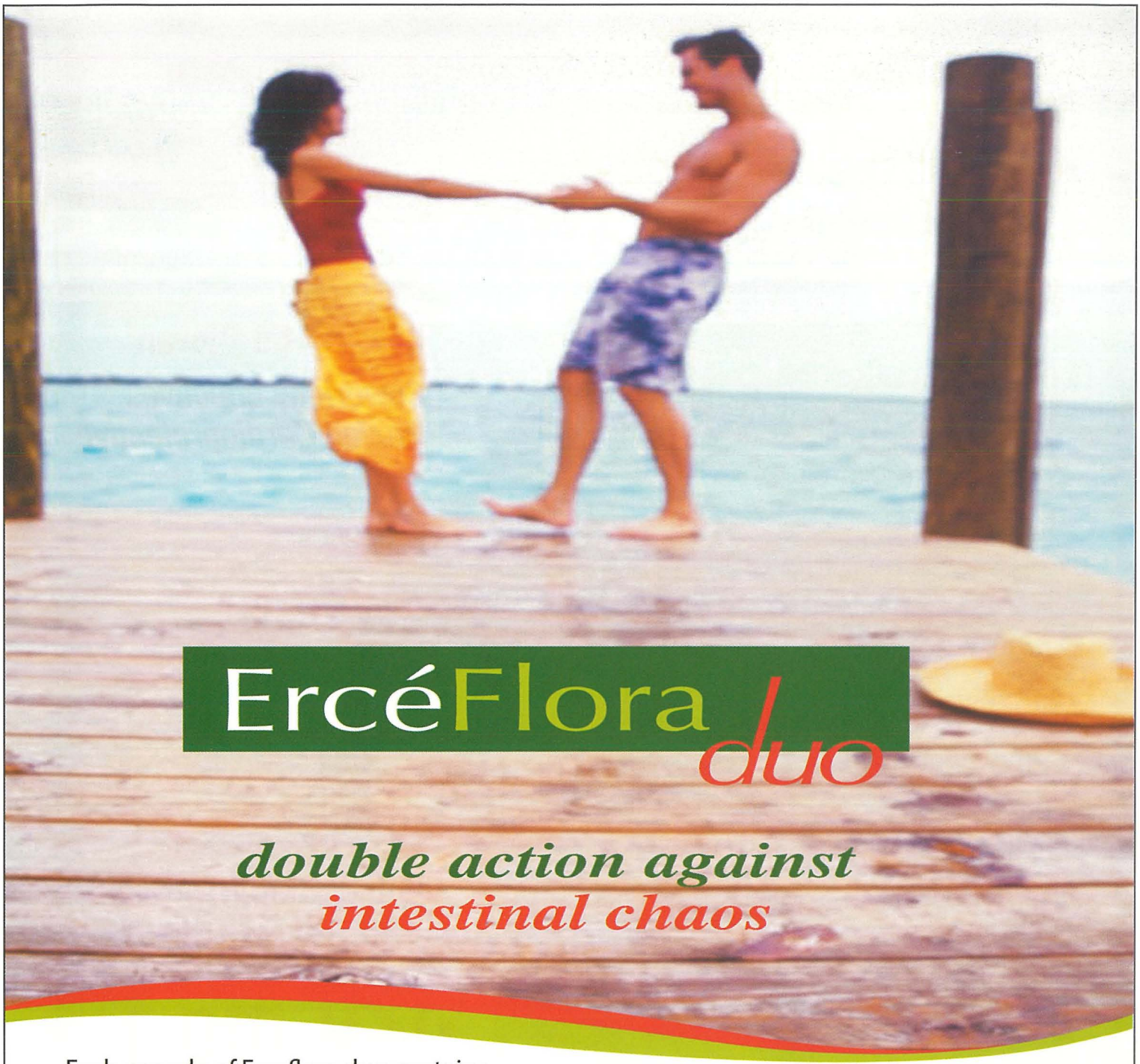
The pharmaceutical industry saw the huge commercial potential in creating drugs that increase brain neurotransmitters, coming up with the tricyclics and monoamine oxidase inhibitors, and more recently the Selective Serotonin Re-uptake Inhibitors (SSRIs). Most have unpleasant side-effects – the ones associated with SSRIs include nausea, insomnia, weight loss or gain, and loss of libido and ability to achieve orgasm. However, out of this morass of conflicting information and worrying treatment options, a revolutionary idea emerged. Professor David Horrobin, a pioneer of omega-3 and omega-6 essential fatty acid (EFA) research, together with Professor Puri, initially discovered that fish oil clears the depression in schizophrenic patients, and Basant Puri went on to research the role of EFAs in other brain function disorders.

Brain imaging has not only identified low brain electrical activity in depression, but Puri's Hammersmith MRI imaging research team also developed a technique which demonstrated *a reduction in grey cortex thickness in depression, and a recovery of cortical thickness with marine EFA eicosapentaenoic acid (EPA) treatment,* adding proof that EPA worked as a treatment for depression.

The most important complex lipid in brain function is phospholipid, because this is partly responsible for the smooth messaging system between neurons, ensuring that the electrical circuits are protected and insulated. If brain cell phospholipids contain predominantly saturated fatty acids, because that is what we are eating, then since saturated carbon chains tend to clump together and react slowly with other molecules, the neuronal membrane and neurotransmitter function becomes sluggish, and the brain's electrical messaging system slows down. However, when neuronal phospholipids are predominantly composed of highly unsaturated EFAs, the carbon chains are much more fluid, and the neuronal membrane neurotransmitter receptors can float freely and work at optimum speed and efficiency, resulting in more successful brain messaging system. The phospholipids found in all cell membranes, and which protect and enhance brain message connectivity, are therefore vital to a healthy brain and avoidance of depression.

So how was EPA found to be the optimal building block for these cellular membrane phospholipids? Horrobin and Puri's trials with fish oils attempted to single out the separate benefits of the various marine EFAs, and began to show that DHA, found in large amounts in the healthy brain but in reduced amounts in the schizophrenic brain, might be the therapeutic winner. But their comparative trials with DHA and EPA on schizophrenics showed that the ones who improved substantially were the ones taking EPA. Their improvement was as good as one might expect with normal anti-schizophrenic drugs, but without any side-effects. One of the associated symptoms of

continues on page 14



ErcéFlora *duo*

double action against intestinal chaos

Each capsule of Erceflora duo contains 3 different components -

2 lactic enzymes and one yeast:

- Lactobacillus rhamnosus 25mg
- Lactobacillus acidophilus 25mg
- Saccharomyces boulardii 100mg

The three strains have a different mode of action and may act synergistically.

Adults & Elderly: 1 to 3 capsules daily
Children 0-2 yrs: 1 capsule daily
2-6 yrs: 2 capsules daily
6 yrs and over: up to 3 capsules daily

Erceflora duo can help to strengthen the intestinal flora:

when taking antibiotics

- *when travelling in hazardous regions*
- *when facing dietary and hygienic changes*
- *when travelling and changing diet.*

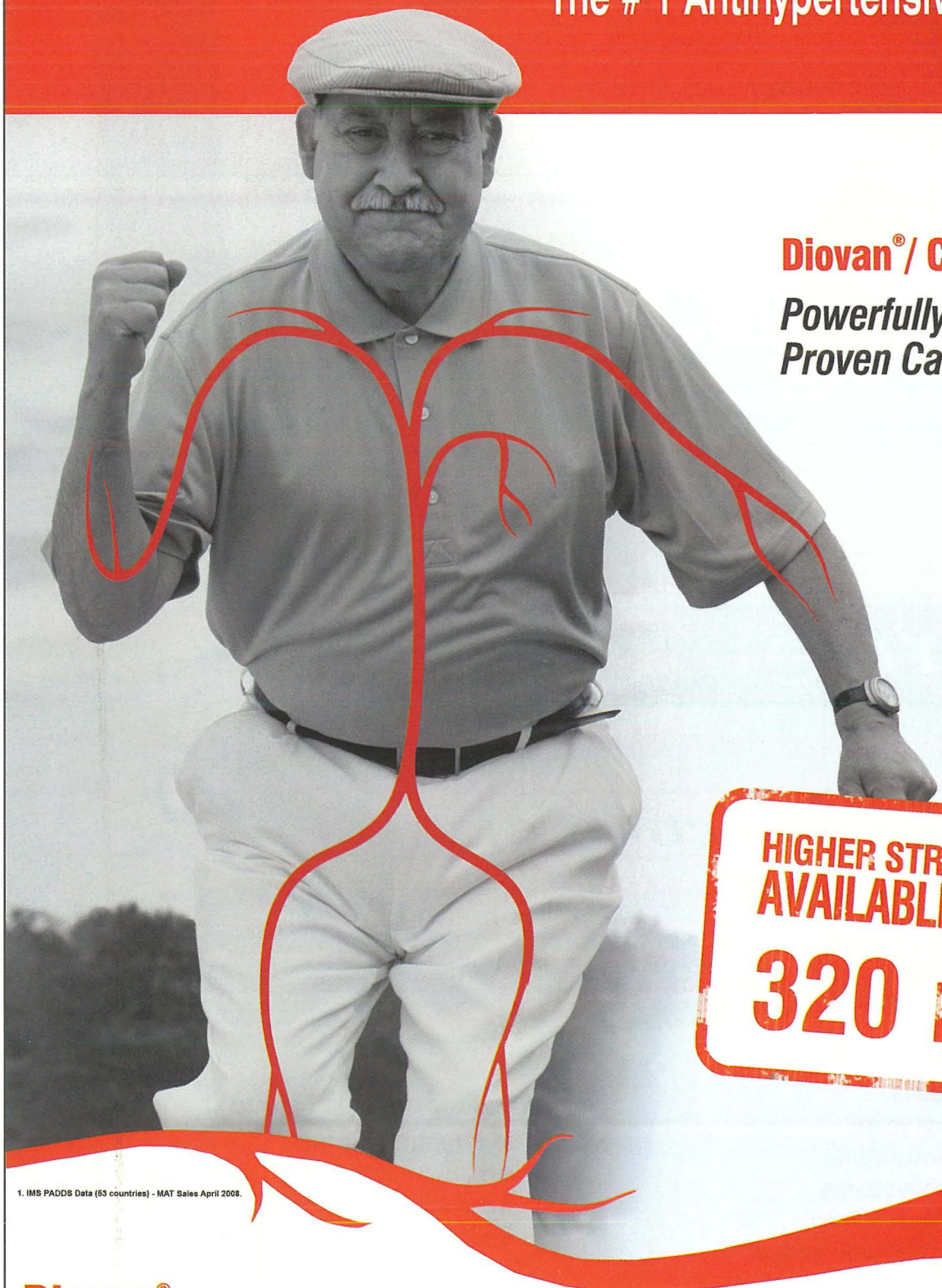
Erceflora duo is a food supplement belonging to the probiotics family that helps to strengthen the intestinal flora.

For further information please contact Sanofi-Aventis Malta ltd on tel no: 21493022

sanofi aventis
Because health matters

MT-SAC-09-03-01

The # 1 Antihypertensive Worldwide[1]



Diovan®/ Co-Diovan®

Powerfully Effective...
Proven Cardioprotective

HIGHER STRENGTHS AVAILABLE NOW

320 mg

1. IMS PADDS Data (53 countries) - MAT Sales April 2008.

Diovan®

Presentation: Valsartan: film-coated tablets of 80 mg, 160 mg and 320mg. **Indication:** Hypertension, post-myocardial infarction, heart failure. **Dosage - Hypertension:** Recommended dose is 80 mg once daily. If the fall in blood pressure is inadequate, dosage may be increased to 160 mg. If additional blood pressure reduction is required, the dose can be increased further to a maximum of 320 mg or another antihypertensive (e.g. diuretic) may be added. **Treatment of post-myocardial infarction:** Starting dose is 20 mg twice daily. Uptitration to a maximum of 160 mg twice daily as tolerated by patient. **Heart failure:** Starting dose is 40mg twice daily. Uptitration to 80 and 160mg twice daily as tolerated by patient. **Contraindication:** Known hypersensitivity to the components of this product, severe renal impairment (creatinine clearance < 10 mL/min), biliary cirrhosis and cholestasis and patients undergoing dialysis, pregnancy. **Precautions/Warnings/Interactions:** Risk of hypotension in sodium- and/or volume-depleted patients. Caution is advised when administering valsartan to patients with renal artery stenosis, hepatic impairment, aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy. Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. Caution should be observed with the triple combination of an ACE-inhibitor, beta-blocker and Diovan. In patients with severe heart failure, treatment with Diovan may cause impairment of renal function. Concomitant treatment with potassium-sparing diuretics or potassium supplements may increase serum potassium levels. Caution is advised when driving or operating machines. Avoid use in women planning to become pregnant and whilst breast-feeding. **Adverse reactions:** Generally similar in incidence to patients receiving placebo in placebo-controlled clinical trials, e.g. headache, dizziness, fatigue. The observed incidence of cough with valsartan in controlled clinical trials was significantly less than that observed with ACE inhibitors and similar to that seen with placebo. **The most common adverse reactions are:** viral infections, postural dizziness (reported in heart failure indication), orthostatic hypotension (reported in heart failure indication), neutropenia, upper respiratory tract infection, pharyngitis, sinusitis, hyperkalaemia (reported in post-myocardial infarction and heart failure indications), insomnia, libido decrease, vertigo, hypotension (reported in post-myocardial infarction indication and uncommon in heart failure indication), cough, diarrhoea, abdominal pain, back pain, fatigue, asthenia, oedema, syncope (reported in postmyocardial infarction indication), cardiac failure (reported in post-myocardial infarction indication). **Very rare adverse reactions but potentially serious are:** thrombocytopenia, hypersensitivity including serum sickness, vasculitis, heamorrhage, angioneurotic oedema (uncommon in post-myocardial infarction indication), renal impairment (common in heart failure indication), renal insufficiency, acute renal failure (uncommon in post-myocardial infarction indication). Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine and potassium, usually minor and transient **Packs and prices:** Country specific. **Marketing Authorisation Holder:** Novartis Pharmaceuticals UK Ltd., Frimley Business Park, Frimley, Camberely, Surrey GU16 7 SR, UK. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma, P.O. Box 124, Valletta, VLT1000, Malta. Tel +356 22983217. 2008-MT-01-Diovan

Co-Diovan®

Presentation: Coated tablets containing 80 mg valsartan (an angiotensin II receptor antagonist) and 12.5 mg hydrochlorothiazide (a thiazide diuretic) or 160 mg valsartan and 12.5mg hydrochlorthiazide or 160mg valsartan and 25mg hydrochlorthiazide or 320 mg valsartan and 12.5mg hydrochlorthiazide or 320mg valsartan and 25mg hydrochlorthiazide. **Indication:** Hypertension. **Dosage:** One tablet of Co-Diovan 80/12.5 mg or 160/12.5 mg or 160/25mg or 320/12.5mg daily or 320/25mg daily. **Contraindication:** Known hypersensitivity to the components of this product or to sulphonamides, pregnancy, severe hepatic impairment, biliary cirrhosis and cholestasis, anuria, severe renal impairment (creatinine clearance < 30 mL/min), refractory hypokalemia, hyponatremia, and hypercalcemia. Symptomatic hyperuricemia. **Precautions/Warnings:** Risk of hypotension in sodium- and/or volume-depleted patients, caution is advised when administering Co-Diovan to patients with renal artery stenosis, renal and liver disease, systemic lupus erythematosus. Disturbance of serum electrolyte balance, glucose tolerance and serum levels of cholesterol, tryglicerides and uric acid. Caution in driving or operating machinery. Avoid use in women planning to become pregnant and while breast-feeding. **Interactions:** Concomitant treatment with potassium-sparing diuretics or potassium supplements may increase potassium levels. Caution if combined with other antihypertensives or lithium (serum lithium monitoring), curare derivatives, NSAIDs, digoxin, antidiabetic agents, allopurinol, amantadine, cytotoxic drugs, anticholergenic agents, cholestyramine, vitamin D, calcium salts and cyclosporine. **Adverse reactions.** headache, dizziness, fatigue. For the hydrochlorothiazide component, other reported adverse reactions include hypokalemia, hyperuricemia and other electrolyte imbalance, postural hypotension and rise in blood lipids. Rare: jaundice, cardiac arrhythmias, blood disorders. Very rare: vasculitis, pancreatitis, pneumonitis, pulmonary edema. Post-marketing experience revealed very rare cases of hypersensitivity (e.g. angioneurotic oedema), and impaired renal function, myalgia and thrombocytopenia. Laboratory findings: Neutropenia, elevations in creatinine and blood urea. **Packs and prices:** Country specific. **Marketing Authorisation Holder:** Novartis Pharmaceuticals UK Ltd., Frimley Business Park, Frimley, Camberely, Surrey GU16 7 SR, UK. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma, P.O. Box 124, Valletta, VLT1000, Malta. Tel +356 22983217. 2008-MT-01-Co-Diovan

NOVARTIS

DIO Ad1 03/09 MT

'GRAPE EXPECTATIONS'

Continuing our Introduction to Wine Enjoyment

Albert Cilia-Vincenti

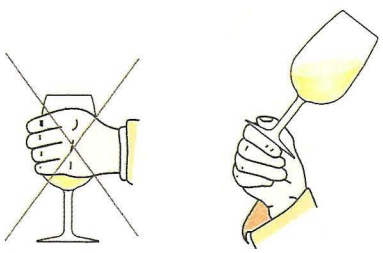
'Wine is a friend, wine is a joy; and, like sunshine, wine is the birthright of all'

(AndrŹSimon, 1877-1970)

Getting back to the two basic questions we need to ask ourselves each time we approach a wine, namely, *"how much do I like it, and why?"*, we need to highlight some important wine characteristics which one has to be conscious of when evaluating a wine.

Tannin – a natural substance which comes from grape skins, stems, pips and from oak barrels used for aging many wines. Red wines usually have higher tannin levels than whites, because red grapes are usually left to ferment with their skins. Tannin is a natural preservative permitting continued wine improvement in the bottle – if a red wine is to be aged to improve over a long time, it must start off with a high tannin level. In young wines, tannin can be very astringent and thus dries the palate, blocking fruity flavours and making the wine taste harsh and austere – although tannin is not actually a taste, but a tactile buccal sensation. To help you identify tannin in wine, rinse a mouthful of cold black tea round your palate and notice how your cheeks react to it. The tannic harshness in a young *Barolo* or immature red *Bordeaux* when tasted without food will disappear if you take wine alongside protein and fat. The wine trade's maxim, *"a food wine"*, indicates a wine that will be best enjoyed when part of a meal. Wine-producing regions with strong culinary traditions that include wine with food, such as those in France, Italy and Spain, tend to make wines like this. Big Australian brands intend their wines to be enjoyed as drinks in their own right, so they may not work as well with food, and are sometimes referred to as *"wine-bar wines"*. These sweeping distinctions between what may also be called *"old world"* or *"traditional"*, and *"new world"* or *"modern"* wine styles, are the source of debate and controversies to which we"ll return in future.

Acidity – all wine has a certain amount of acidity. White wines usually have more acidity than reds, although winemakers try to balance the fruity flavours and acid. If you are unsure what exactly is acidity, smell and then taste lemon juice or vinegar. Although the mention of acidity can be off-putting for beginners, with connotations of sourness and harshness, it is a vital part of the wine's structure, holding the flavours together and balancing the other components, making it a refreshing drink, and also acting as a preservative. If the acidity is too high, the wine is unbalanced, tart or sour and harsh but, if too low, the wine will taste flat with loss of flavours and will not age well.



This isn't how a wine taster holds a glass.

Now you can observe the whole range of colours in the glass.

Body, mouthfeel and alcohol – *body*, or *mouthfeel*, of a wine is an assessment of how light or heavy the wine feels in the mouth – generally related to alcohol levels, with more alcoholic wines feeling heavier on the mouth than cooler climate wines where alcohol level is lower. Very high alcohol levels (14% and above) can give a sweet flavour to wine, which is why some very ripe wines can appear sweeter even though analysis proves they are dry.

Balance – acidity is vital to the balance of wine's flavour and structure. A balanced wine is one in which none of its components dominates. Sweet wines need a higher acidity if they are to be well balanced. A sweet wine with low acidity will be sickly and cloying, whereas one with high acidity will finish clean without that overly sweet character.

Albert Cilia-Vincenti is a long-standing member of the UK's Wine Society (1874), and founding committee member of 'Il-Qatra' blind-tasting wine-lovers' club of Malta. He may be contacted on *acvincenti@onvol.net*.

Professor Basant K. Puri's Medical School Talk – Part II
Fatty Acids, Depression, Schizophrenia & Huntington's Disease

continued from page 10

schizophrenia – depression – was also noticeably improved following EPA treatment. EPA was chosen as the most successful of the EFAs for treating even serious depression. It worked at least as well as, and in many cases much better than, standard antidepressant drugs, but without the side-effects these powerful drugs might impose.

Which diet and lifestyle habits might strip EFAs from the body, or hamper conversion of EFAs into the phospholipid layer?

Although these habits do not necessarily cause depression – many people who eat an extremely unhealthy diet never succumb to depression – they are a strong contributory factor to making the body's biological environment ripe for a depressive episode if other factors are in place to trigger it. These negative habits include a diet rich in saturated fat, trans-fatty acids and sugar, high alcohol consumption, cigarette smoking, and a lack of nutrients such as zinc, selenium and vitamin B_6 as might happen with constant harsh dieting. Trans-fatty acids are produced in significant amounts when previously healthy unsaturated vegetable oils are heat-hardened to make margarine and non-dairy cream used in commercial cakes and biscuits.

Basant Puri's MRI imaging research team were not only the first to develop MRI software to measure changes in brain volume and cortical thickness, but also the first to develop magnetic resonance spectroscopy enabling study of brain fatty acid chemistry, i.e. what was happening to neuronal EFAs. Results were extraordinary. Conventional medical wisdom had long dictated that adult brain tissue has no regenerative growth capacity, so the finding that *depressive brains regained volume and cortical thickness with EPA treatment* came as a complete surprise. As the grey matter is the home of neurons and neurotransmitters, if it is shrunken and unhealthy there will be fewer neurons and less mobile receptors for mood-enhancing neuro-transmitters, so serotonin levels will fall and depression may set in. When the grey matter is enriched and healthy, there will be greater abundance of healthy neurons and higher neurotransmitter levels, thus lifting depression.

Recent studies showing brain regeneration in rats induced by brain exercise, and seasonal variation in song-bird brain size (increase in size in singing season), support the view that brains are capable of growth. In the case of EPA treatment and the MRI brain size and cortical thickness changes, it is thought, although this is not yet certain, that EPA stimulates brain tissue stem cells.

Basant Puri's MRI research team have also discovered that women's brains shrink in the last three months of pregnancy, probably because the foetus is scavenging the mother's EFAs to assist its own brain development. Postnatal maternal brain scans show a gradual brain re-growth. Pregnancy is therefore a time when a good supply of EFAs to the mother's body is particularly essential, and EPA supplementation thus helps prevent postnatal depression. The mother's EPA supplementation, combined with breast-feeding, will also enhance the baby's general health and brain development.

Puri's MRI techniques have also demonstrated that *EPA treatment regenerates the schizophrenic brain* in a similar fashion to the depressive brain, besides other benefits, such as improved reading, spelling, fluency and comprehension. He has also shown that *EPA supplementation in Huntington's disease also regenerates to some extent brain tissue, with a reduction in its symptoms.*

Bibliography

1. De Vriese SR, Christophe AB, Maes M. In humans the seasonal variation in poly-unsaturated fatty acids is related to the seasonal variation in violet suicide and serotonergic markers of violet suicide. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2004; 71:13-18.
2. Hibbeln JR. Fish consumption and major depression. *Lancet* 1998; 351:1213.
3. Nemets B, Stahl Z, Belmaker RH. Addition of Omega-3 Fatty Acid to Maintenance Medication Treatment for Recurrent Unipolar Depressive Disorder. *American Journal of Psychiatry* 2002; 159:477-479.
4. Neuringer M, Anderson GJ, Connor WE. The essentiality of n-3 fatty acids for the development and function of the retina and brain. *Annual Review of Nutrition* 1988; 8:517-541.
5. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives of General Psychiatry* 2002; 59:913-919.
6. Puri BK, Counsell SJ, Hamilton G, Richardson AJ, Horrobin DF. Eicosapentaenoic acid in treatment-resistant depression associated with symptom remission, structural brain changes and reduced neuronal phospholipids turnover. *International Journal of Clinical Practice* 2001; 55:560-563.
7. Puri BK, Counsell SJ, Richardson AJ, Horrobin DF. Eicosapentaenoic acid in treatment-resistant depression. *Archives of General Psychiatry* 2002; 59:91-92.
8. Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind placebo-controlled trial. *European Neuropsychopharmacology* 2003; 13:267-271.
9. Zimmer L, Vancassel S, Cantagrel S, et al. The dopamine mesocorticolimbic pathway is affected by defieciency in n-3 polyunsaturated fatty acids. *American Journal of Clinical Nutrition* 2002; 75:662-667.

Prof Cilia-Vincenti is a former London University Recognised Teacher at Charing Cross and The Middlesex Hospital Medical Schools, and a former teacher at Malta's University Medical School. He maintains a longstanding interest in the health and longevity consequences of nutrition. He may be contacted on acvincenti@onvol.net.

Update on Avian Influenza

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

2009, like in previous years, has seen the reoccurrence of confirmed human avian cases with 7 cases in China (4 died), 4 cases in Egypt, 2 cases in Vietnam and also 2 cases in Indonesia (both died).

The occurrence of 5 human cases of avian influenza in a three week period in China in January, were one could possibly have been a mother-to-child transmission, with no corresponding reports of avian flu outbreaks, was seen as a cause of concern. The most likely explanation was that the human cases were exposed to H5N1 infected poultry, which were excreting the virus, but since they had been vaccinated against avian flu were showing no symptoms of disease.

Seasonal Influenza

Influenza activity has continued to increase during January and February across central Europe, following a west-to-east trend, with declining activity in western Europe whilst continuing to remain low in eastern Europe.

Type A(H3N2) continues to be the dominant influenza virus circulating in Europe. Antigenic and/or genetic characterisation indicates that the viruses circulating are similar to the three components (A(H1N1), A(H3N2) and B/Yamagata lineage) included in the current influenza vaccine. Although low numbers of influenza B viruses are circulating, there has been a continuous increase in February.

All influenza A(H3N2) viruses tested in Europe for antiviral resistance were resistant to M2 inhibitors but susceptible to neuraminidase inhibitors. The few influenza B viruses analysed were also found to be sensitive to oseltamivir and zanamivir but high resistance was found in influenza A(H1N1) viruses to oseltamivir.

A human case of swine influenza virus infection in Europe

Humans in contact with pigs occasionally become infected by swine influenza viruses. This has occurred in a middle-aged woman in Spain this January. The woman worked with pigs and suffered a mild self-limiting influenza-like illness. A swab taken showed that it was influenza A(H1N1) phylogenetically similar to European H1N1 swine influenza virus. Retrospective epidemiological investigations found no evidence of any further cases apart from her family doctor who had experienced similar symptoms but was not laboratory-confirmed.

Swine are susceptible to the same influenza A virus subtypes as humans – H1N1, H3N2 and H1N2. Many swine influenza viruses are a result of reassortment and their genes are composed of human and avian and/or swine virus genes. It is a known fact that both human and avian influenza viruses occasionally transmit to pigs and that pigs can serve as 'mixing vessels' for these viruses, which means that viruses can exchange genetic material and lead to the production of a new 'hybrid' virus.

Influenza is one of the major causes of acute respiratory disease in pigs. The symptoms and pathogenesis of influenza in pigs show remarkable similarities with those of seasonal influenza in humans, but the epidemiology is different. Unlike human viruses, swine influenza viruses circulate at comparable levels all the year round.

Infection with swine influenza virus has been detected sporadically in humans since the 1950s but has been found to be much milder that those seen with avian A(H5N1).There have also been reported cases of single generation person-to-person transmission but are rare.

A study on the efficacy of soap and water and alcohol-based hand-rub preparations against live H1N1 influenza virus on the hands of human volunteers

This study was done to verify the most effective methods that can be used to eliminate influenza viruses on human hands. Five methods were used: A control (where no hand hygiene took place); washing with soap and water; and washing with 3 alcohol-based solutions with increasing alcohol concentrations. The concentrations of influenza A(H1N1) virus on the hands of the volunteers as well as the natural viability of H1N1 on the hands for more than 60 minutes without hand washing protocols were calculated before and after each treatment by means of viral culture and quantitative real-time reverse-transcriptase polymerase chain reaction (PCR).

The results of the study found that there was a rapid reduction in culture-detectable and PCR-detectable A(H1N1) after a short (2 minute) period of cutaneous air drying alone. There was also minimal further reduction in detectable H1N1 virus after 60 minutes without washing. The antiviral efficacy for all four hand washing protocols was high with all four hand-washing protocols. Washing with soap and water was statistically superior to the three alcohol-based treatments, although the difference was small.

This means that both soap and water and alcohol-based wipes, if used appropriately, will reduce the risk of influenza transmission through hands. However one must not forget that although hands can account of transmission of influenza, the main form of transmission is droplet and aerosol transmission.

Checkmate

by **Marika Azzopardi**

What do chess and rheumatology have in common? Not much at face value except that they are both part of the life of Dr Andrew Borg, Consultant Rheumatologist at Mater Dei and champion chess player. How did it all come about, fall in place? Certainly one square at a time.

On the professional front, Dr Borg travelled to the UK in 1988 to proceed with his studies. He found himself as a registrar in General medicine in Stoke-on-Trent where he met a Rheumatologist by the name of Dr Ted Hothersall. "He was a consultant there and he highly encouraged me to take up this speciality, following and directing me through my career ever since. He happened to be a frequent visitor to Malta and was a good friend of dermatologist Professor Joe Pace. I took up a registrar's post with him and he was constantly very supportive of me and my young family since we had a three-month-old daughter at the time."

Because of the situation in the mid-eighties where the Maltese medical degree only had partial recognition in the UK, he could not go into a surgical speciality easily. However he could go into a medical speciality and it seemed the ideal one to follow.

His interest in water polo which he had practised back in Malta for many years, winning three National Championships with Sliema ASC and another two with Exiles, as well as a two year stint with Newcastle Paragon in the UK contributed to his decision to take up rheumatology. "Since I knew sport injuries well (having sustained rib, finger and nose fractures, shoulder tears and hip injuries during my water polo career!), I was personally interested in the treatment and outcome of sport-related musculoskeletal problems."

After six years studying in the UK and 10 years practising as a Consultant Rheumatologist in South Wales, Bath and Basingstoke, Dr Borg returned to Malta in 2004.

Today the bulk of his patients tend to be older patients whose bodies experience varied musculoskeletal problems, back and neck pain, osteoarthritic problems, osteoporosis and the like. However his specific area does not concentrate solely on treating elderly patients, as arthritic and rheumatoid conditions are also to be found in children who are unfortunately, all too often, under-diagnosed. In this regard, Dr Borg runs a monthly paediatric rheumatology clinic which adds to his loaded burden. In between talking of his family – his wife Mariella who is a consultant in public health medicine and his two children, Renee - nineteen (presently studying to be a vet), and Matthew - seven, we approach the topic of chess. Dr Borg explains how it all began way back in 1976, when he was, along with his brother, roped in with the Gzira Chess Club. "We were both introduced to the game by my father who decided it was the ideal activity to keep us both out of mischief!"

However, it turned into something beyond that. By 1978 he won the Malta

Published with kind permission of Dr Andrew Borg

on joints

Junior Championship; in 1980 he won a silver medal at the World Team Championships with future World Champion Garry Kasparov bagging the bronze! He represented Malta on a number of subsequent occasions until going up to the UK. After giving up chess completely for a number of years he restarted playing in 2000 in the World Team Championships in Turkey. But it was only in 2004 when he returned to Malta that he resumed active competitive chess, winning the Malta championship at the first time of asking, and was runner-up in the following two years. Unfortunately both in 2007 and 2008 he was unable to play due to work commitments. "Chess is like a virus. You either have it or you don't. There is a beauty in making things work and helping them to fall neatly into place. One eminent mathematician compared chess to solving algebra. He said that his initial aim was to solve the problem. However if the solution was not a beautiful one, then it must be incorrect. I feel this epitomises the game of chess excellently."

Ideally an expert chess player would spend seven hours a day at the game, each day of the week. As things stand, he doesn't manage to play every day, except for the odd hour after all the family is asleep. But is he a patient man? "I wouldn't say chess has anything to do with patience. It is more about dedication and being focused. Quite frankly all chess players tend to be professionals, players who are used to discipline, to following clear-cut rules. Chess players must also be very fit because it takes quite a good level of fitness to endure long games of concerted mental effort. This is clearly an area I need to work on!"

The internet has opened new horizons in chess enabling one to find opponents from all corners of the world. However, none of these games are serious and are usually 3 minute or 5 minute games, hardly serious preparation for world ranking competitions.

In Malta he reckons there is a very limited pool of strong players, seven or eight at most. "This means we have to travel abroad to confront new, strong opponents. The Malta Chess Federation presently has some 200 members, many of whom are quite young. Additionally there is an active schools' programme which is striving to generate new and strong chess players, so the future of Maltese chess looks promising."

And so, in between injecting painful joints, backs and necks, Dr Borg relies on chess to ease his own tense muscles. It is certainly one sport which can be practised for many years even after physical sport is contra-indicated … and not necessarily because of painful joints, spines and backs.

As Dr. Borg said "chess players never die young ... they know all the right moves !"

Ordinary and Extraordinary Treatment: a case for review?

by **Pierre Mallia** *MD MPhil PhD MRCP FRCGP*
Bioethics Research Programme
Medical School, University of Malta

The recent Englaro case has again given rise to the controversy of keeping a person alive in a persistent vegetative state (PVS) by nutrition and hydration through a nasogastric tube. The last controversial case which made a similar outcry was that of Terry Sciavo in the United States. The question to consider is whether nutrition and hydration, especially after several years in a PVS constitutes an ordinary measure to keep a person alive or an extraordinary and/or heroic one.

The difference between Ordinary / Extraordinary treatment originates from Roman Catholic Medical Ethics and was introduced by Pope Pius XII in the 50s, as a guidelines to Catholics in the face of new extraordinary means to keep people alive which were becoming more and more common. In fact before being able to keep people alive on a life support system, one was considered dead when one's heart stops beating. (This still applies for medico-legal purposes, say, when one attempts cardiac resuscitation – if the attempt fails one cannot be accused of having caused death). A Harvard neurologist introduced the Brain Death Criteria, to determine whether a person is still scientifically alive and therefore allowing removal of the body from advanced life support.

The first controversial case, ironically, was to put a girl *off* life support when she was in fact not yet brain dead[1]. Mary Quinlan was a 21 year old on life support. She had been involved in an accident. She also was Roman Catholic as were her parents. The parents thought that keeping her alive on such a system was something they could not bear. They wanted her to die in dignity. Their Parish Priest defended their case. The doctors however would not agree as she was not brain dead. The case went to court, which made historical ground when it was decided that the criteria of a social institution (in this case the Catholic religion) could over-ride scientific thought. She was subsequently removed from life support and allowed to die *even though she was not brain dead.*

At this juncture it is important to note that the definition of the Church, subsequently put through scholarly rigour[2] takes note of two particular (and important) points. First, what is to be defined as ordinary or extraordinary has nothing to do with the state-of-the-art medicine used in such cases. Blood transfusion was then considered as quite an extraordinary form of treatment. Today it is very common place. Yet we still note the controversy over Jehovah Witnesses, which to them is an extraordinary measure. What is ordinary for one person, such as having CPR, may be considered extraordinary for another. In this regard, having an Advance Directive (or living will) can be very helpful.

This brings up the second point – the relatives. The burden of the relatives is considered very important in determining whether treatment is ordinary or extraordinary. Therefore if the relatives have to go through extraordinary measures, such as selling a house, or extreme psychological distress, as in the Quinlan Case, then the treatment is considered extraordinary.

... if the relatives have to go through extraordinary measures, such as selling a house ... then the treatment is considered extraordinary

It is here that cases become controversial, although in reality they should remain confidential. The fact that respect for confidentiality seems not to take place here implies that we are still in an evolutionary phase of understanding these cases, and there is still to be found a balance between what is important to the patient/relatives, and what is important to society.

Roman Catholic moralists have however traditionally argued, as in the Quinlan case, that moral obligation demands only the use of 'ordinary' means:

Extraordinary means of preserving life are all medicine, treatments, and operations, which cannot be obtained or used without excessive expense, pain or other inconvenience for the patient or for others, or which, if used, would not offer a reasonable hope of benefit to the patient.[2]

Whilst it is important to note that the statement, accepted as 'dogma' nowadays, as it follows directly from the declaration of Pope Pius XII, includes 'others'. The Quinlan case showed how true to the word this is. When it comes to nutrition and hydration however there is still controversy among ethicists.

Many ethicists consider nutrition and hydration to be so basic as to always constitute an 'ordinary' measure. Just as much ethicists however still believe that this is not the case. These arguments arise on whether to *start* a person in a PVS on hydration and nutrition. Definitely a person in such a state cannot be considered to experience hunger in the psychological state. Any nutrition and hydration does not give any satiety or satisfaction. It is simply to keep the physiological status of the body. The Englaro case showed, as opposed to the Sciavo case, how much life can be being held on a thread with nutrition. Jonsen, Siegler and Winslade, following Catholic moral teaching, propose that since controversy exists, both positions are ethically permissible and there is legal ground for both[3]. Certainly, Jonsen is a renowned Catholic theologian in the U.S.

What is unfortunate about these cases is that all forms of confidentiality are lost; people become overly emotional and judgemental about the relatives, and the application of the moral rule of what constitutes extraordinary is lost to public scrutiny and opinion. Some countries may decide to legislate to make things easier. This of course will remove one's right to having advance directives about one's own care, which seemed to be the issue in this case as well.

There will hopefully come a time when we can have a structure which protects both patients and family, keeping the dignity of the situation. This would have to include some form of scrutiny to avoid abuse. Certainly if we decide that both options (giving or withholding nutrition and hydration) are both morally permissible, such policing would not be necessary. For many, living in a PVS for over seventeen years is extraordinary in itself. Other than contact with the person who feeds them two or three times a day, these people usually remain alone all day.

continues on page 22

CryoPen,
Removing skin lesions in a few seconds.

Impressive results in the removal of warts and skin lesions. Safe, effective and easy to work with and comfortable for the patient.

NEW CryoPen|c

CryoPen|c

- very economical 8g gas cartridges
- dosage with pinpoint precision
- standard set with 1 micro-applicator
- reassuring design for young patients

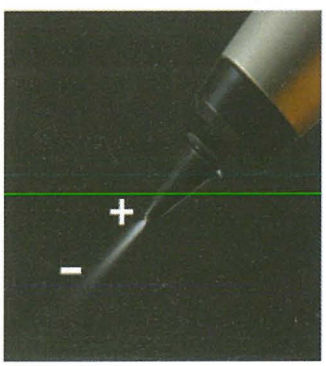
The CryoPen|c is accurate to the millimeter so that the disavantage of collateral tissue damage resulting in blisters and pain is minimized. CryoPen|c allows better penetration to avoid repeated treatments for the patient. It is very suitable for the use on children. CryoPen|c was designed to optimize treatment of warts, keratosis, fibroma, condyloma, lentigo, ...

CryoPen|x

- comes with 3 micro-applicators
- sleek and refined design
- operates with 8g and/or 16g cartridges
- intuitive comfort at a fingertouch

The innovative concept of CryoPen|x allows you to work with pinpoint precision and with minimal discomfort for the patient. No follow-up care and short recovery period. So easy to work with, you activate your CryoPen|x by simply touching the switch.

NEW CryoPen|x



CryoPen®

Applications
1-3mm

Applications
2-5mm

Applications
4-8mm

Fatty liver – Wha

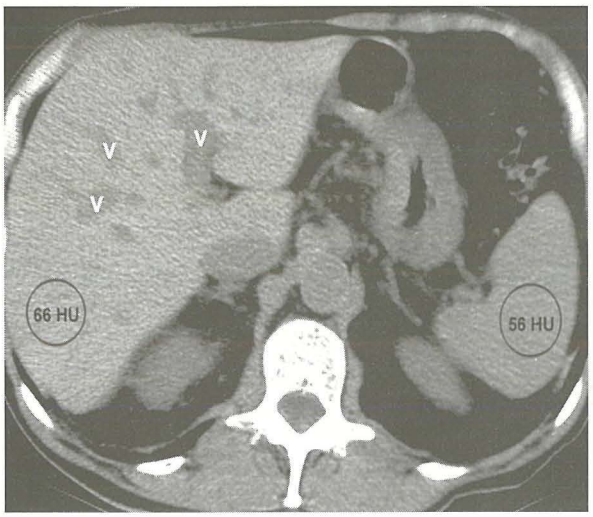


Figure 2. *Normal density of the liver at unenhanced CT (66 HU) is slightly higher than that of the spleen (56 HU), and intrahepatic vessels (v) appear hypodense in comparison with the liver.*

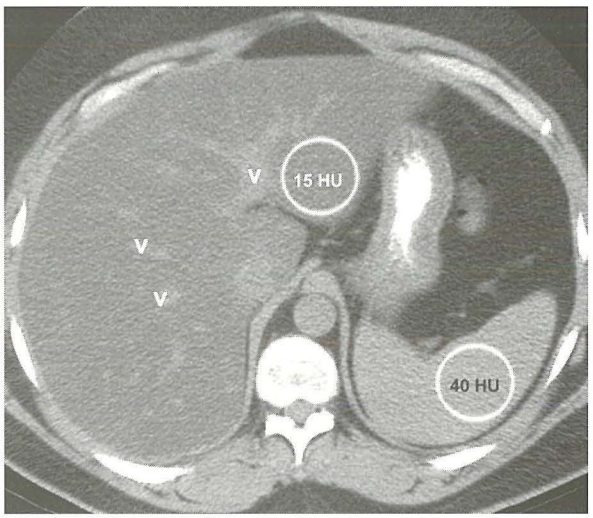


Figure 4. *With diffuse fat accumulation in the liver at un-enhanced CT, the density of the liver (15 HU) is lower than that of the spleen (40 HU) and intrahepatic vessels (v) appear hyperdense in comparison with the liver.*

continued from page 1

Fatty liver may be diagnosed if liver echogenicity exceeds that of renal cortex and spleen and there is loss of definition of more posterior portions of the liver due to beam attenuation (Figure 2).

At unenhanced computed tomography (CT), the normal liver has similar density that the spleen or blood (Figure 3). A liver density less than 40 Hounsfield Units (HU) or more than 10 HU below that of the spleen, is diagnostic of fatty infiltration. In cases of severe fatty liver, the vessels may appear denser (whiter) than the liver parenchyma (Figure 4). Following IV contrast enhancement, comparison of liver with spleen or vessel density is unreliable due to difference in tissue contrast enhancement in different phases of perfusion.

At MR imaging, chemical shift gradient-echo (GRE) imaging with in-phase and opposed-phase acquisitions is the most widely used technique for the assessment of fatty liver. The signal intensity of the normal liver parenchyma is similar on in-phase and opposed-phase images. Fatty liver shows loss of signal intensity (ie becomes darker) on opposed-phase imaging and loss of signal is proportional to the extent of fat deposition. A simplistic explanation for this phenomenon is that during in-phase imaging, the signals of fat and water protons are in phase and both contribute positively to tissue brightness (Figure 5 a), while on opposed-phase imaging, fat signal is negative compared to water signal and cancels it out resulting in dark parenchyma (Figure 5b).

Less common patterns such as focal fat deposition and diffuse fat deposition with focal sparing characteristically occurs in specific areas; these areas are adjacent to the falciform ligament or ligamentum venosum, in the porta hepatis, and in the gallbladder fossa. This distribution has been attributed to variant venous circulation, such as anomalous gastric venous drainage. Focal fat deposition adjacent to insulinoma metastases also has been reported and is thought to be due to local insulin effects on hepatocyte triglyceride synthesis and accumulation.

The diagnosis of focal fat deposition and focal sparing is more difficult than that of homogeneously diffuse fat deposition because imaging findings may resemble mass lesions. Imaging findings suggestive of fatty pseudolesions rather than true masses include (a) fat content confirmed on opposed-phase MR imaging,

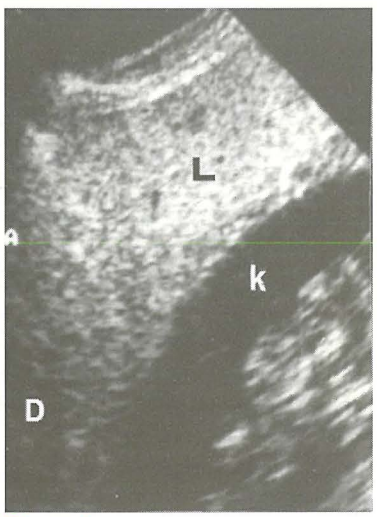


Figure 3. *With diffuse fatty infiltration of the liver, the liver (L) shows increased echogenicity compared to the renal parenchyma (K) and there is loss of definition of the deeper portions of the liver due to beam attenuation (D).*

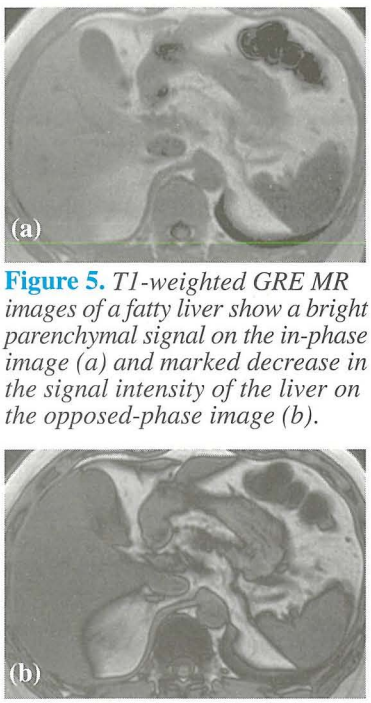
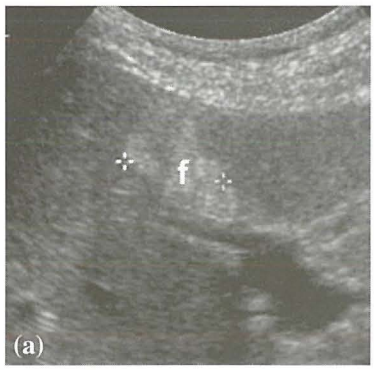


Figure 5. *T1-weighted GRE MR images of a fatty liver show a bright parenchymal signal on the in-phase image (a) and marked decrease in the signal intensity of the liver on the opposed-phase image (b).*

t does this mean?



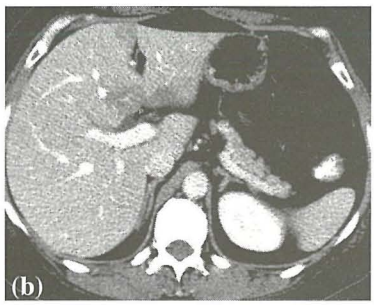
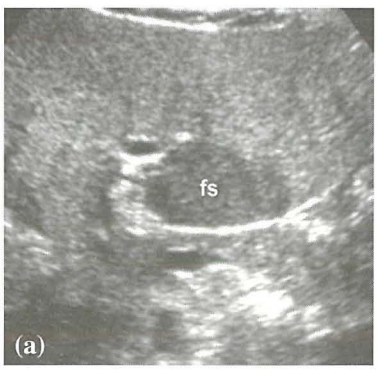


Figure 6. *(a) Transverse US image shows a geographically shaped hyperechoic area (asterisks) anterior to the left portal vein and around the falciform ligament (f). (b) CT scan showing foci of fatty infiltration (darker areas) next to the falciform ligament (f) and anterior to the porta hepatis (p).*



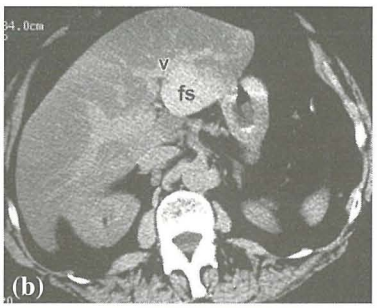
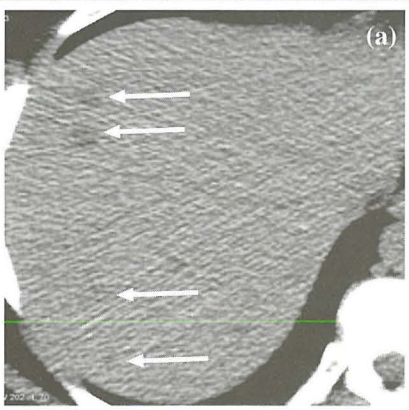
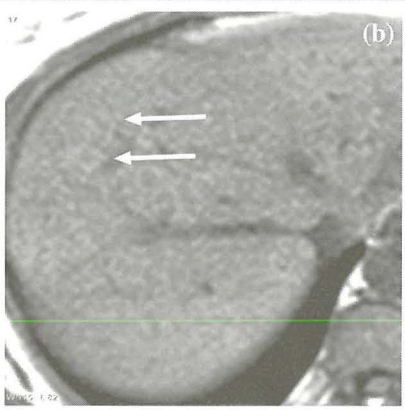


Figure 7. *(a) US image of a diffusely fatty infiltrated liver with focal sparing (fs). (b) Unenhanced CT image shows the area of focal sparing (fs) as hyperdense compared to the remaining diffusely fatty liver. The area of focal sparing exerts no mass effect on the adjacent vessel (v).*





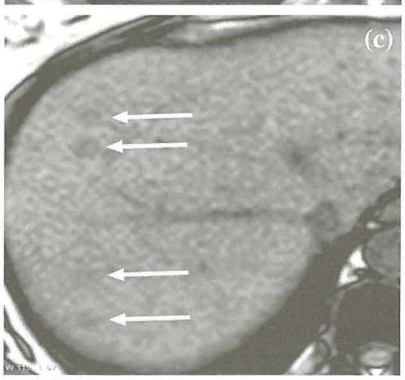


Figure 8. *(a) Multifocal fat accumulation in the liver appears as hypodense foci on unenhanced CT scan in a 48-year-old woman with breast cancer was misdiagnosed as liver metastatic disease on the basis of CT findings. T1 weighted GRE MR images show nodules (arrows) with signal intensity slightly higher than that of the normal liver parenchyma on the in-phase image (b) but with a signal intensity loss on the opposed-phase image (c); this confirms the diagnosis of multifocal fat accumulation.*

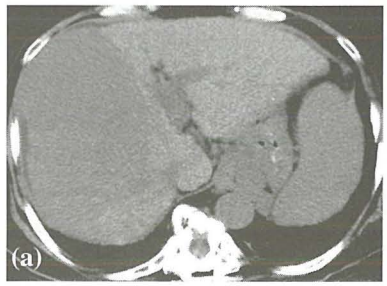
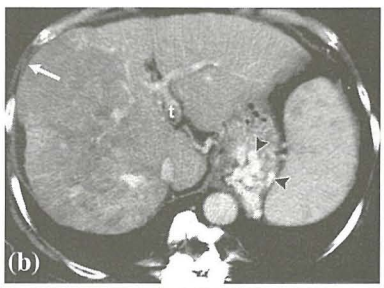


Figure 9. *The hypodense area in the right liver lobe on unenhanced CT (a) may prompt the diagnosis of focal fatty infiltration, however scans obtained during the portal venous phase of IV contrast injection (b) show a nodular liver contour suggestive of cirrhosis, as well as large gastric varices (arrowheads), mass effect with bulging of the anterolateral border of the right liver lobe (arrow), the mosaic enhancement pattern, and the thrombus (t) in the left main portal vein, which are strongly suggestive of an infiltrative hepatocellular carcinoma.*



(b) typical location in areas characteristic of fat deposition or sparing, (c) absence of a mass effect on vessels and other liver structures, (d) a geographic configuration (wavy outline) rather than a round or oval shape, (e) poorly delineated margins, and (f) contrast enhancement that is similar to or less than that of the normal liver parenchyma. The fatty foci are hyperechoic on US and hypodense on CT compared to surrounding liver parenchyma (Figure 6). As expected, the situation is reversed with focal sparing in a diffusely fatty liver, with the spared focus being hypoechoic on ultrasound and hyperdense on CT (Figure 7).

Multifocal fat Deposition is an uncommon form of fatty liver, where multiple fat foci are scattered in atypical locations. The foci may be round or oval and closely mimic true nodules.

continues on page 22

Fatty liver – What does this mean?

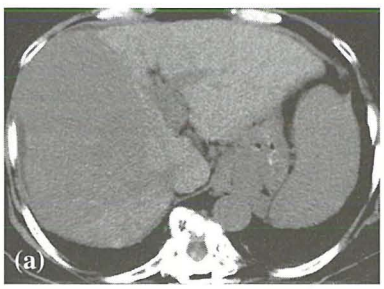
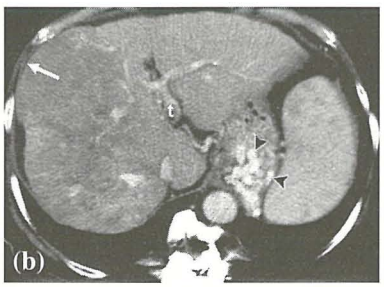


Figure 10. *In a woman with a long history of oral contraceptive use in-phase (a) and opposed-phase (b) T1-weighted GRE images show loss of signal in two left lobe liver lesions (arrows) in opposed-phase image suggestive of focal fatty infiltration. However T1-weighted GRE images obtained during the hepatic arterial phase of IV contrast injection (c) show enhancement of the masses. The location of the lesions is atypical for regions of focal fatty infiltration. The two masses remained stable in size for several years and most likely are adenomas.*



continued from page 21

Correct diagnosis is difficult, especially in patients with a known malignancy, and requires the detection of microscopic fat within the lesion with chemical shift GRE imaging, which is more reliable in these cases than CT or US (Figure 8). Other clues indicative of multifocal fat deposition are lack of a mass effect, stability in size over time, and contrast enhancement similar to or less than that in the surrounding liver parenchyma. Multifocal fat deposition may be observed within regenerative nodules in some cirrhotic patients, where foci of fat accumulation correspond to the fat-containing regenerative nodules.

The differential diagnosis of the different types of fatty liver from malignant lesions may not be so easy. Primary liver lesions such as hepatocellular carcinoma (particularly the infiltrative type) (Figure 9) and hepatic adenoma (Figure 10) may closely resemble focal fatty infiltration. While multiple hepatic metastases in a fatty liver, may be mistaken as areas of focal sparing (Figure 11).

To help prevent diagnostic errors and guide appropriate work-up and management, one should be aware of the different patterns of fat accumulation in the liver, especially as they are depicted at ultrasonography, computed tomography, and magnetic resonance imaging. In addition, knowledge of the risk factors and the pathophysiologic, histologic, and epidemiologic features of fat accumulation may be useful for avoiding diagnostic pitfalls and planning an appropriate work-up in difficult cases. Finally, should the diagnosis remain unclear, one should not hesitate to perform imaging-guided core biopsy of the suspicious area.

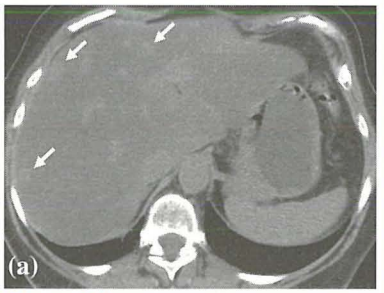
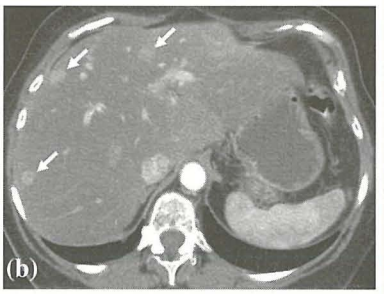


Figure 11. *Pre (a) and post-IV (b) contrast CT scans showing metastases in a fatty liver in a woman undergoing chemotherapy for breast cancer. Multiple round lesions (arrows) enhanced more vividly than the liver parenchyma.*



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

Ordinary and Extraordinary Treatment: a case for review?

continued from page 18

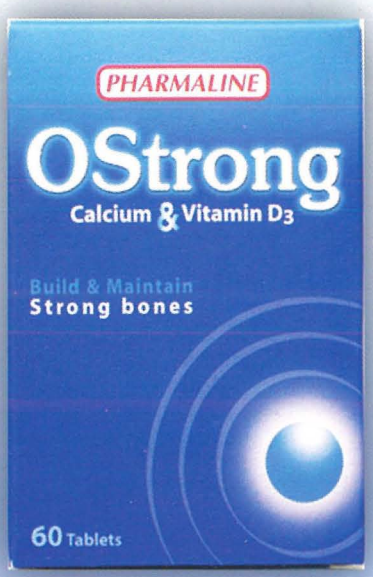
There is a growing literature and evidence on people in PVS. Some drugs have been shown to improve their condition and even bring them back to a relatively normal life. Classifications are continuously developed with further understanding. Indeed many do recover within the first six months. After that the chances are very slim and deteriorate with time. There are exceptional cases and it may be the case that one will be able to identify these with further knowledge on these cases obtained by the use of imaging techniques. There is certainly not enough evidence at the moment and one has to respect that there is an evolutionary phase for both definitions (ordinary and extraordinary treatments). Does nutrition in cases of PVS become extraordinary after a few years? Should we allow the person to die in dignity or leave them in this abyss, if abyss it is?

Conversely PVS has been around since the early seventies, when it was described by a neurosurgeon from Scotland. It is a side-effect of modern medicine, and we are still in the evolutionary phase of understanding even the classification, let alone the state itself. In the meantime should we be 'prudent' and give physiological feeding to these people and keep them in this abyss for seventeen years; or should we build an evidence-based literature which guides us as to when, early in the process, feeding would be considered extraordinary? For the family it is always difficult, but as with life support systems, there will be those who, as in the Quinlan case, would see any advancement as a technology which interferes with the natural dying process. There will be others who, even after the relative is brain dead, will object to the removal, thinking that since their heart can be kept beating, then there is still the possibility of a miracle. We have moved forward with life support systems, and chances are that we will move forward in PVS.

References

1. Baker R. The History of Medical Ethics, in Porter R, Bynum WF (Eds), Companion Encyclopedia of the History of Medicine, Vol 2, Routledge, London. 2004:875-878.
2. Kelley G. Medico Moral Problems. St. Louis, Catholic Hospital Association, 1958:135.
3. Jonsen AR, Siegler M, Winslade W. Clinical Ethics 2nd ed. Macmillan, New York. 1986:110.

"Calcium supplementation reduces risk for all fractures and minimal traumatic fractures in healthy adults younger than 80 years" [1]



+ *Easy to swallow, especially in pregnant and elderly patients*
+ *Combination ensures maximum absorption of Calcium*
+ *Excellent Price*

Composition: *Each tablet contains 600mg Calcium phosphate & 500 IU Vitamin D3.*
Recommended daily dosage: *Pregnant & Lactating women, 1 tab daily; Pre/post menopausal women, 1-2 tabs daily; Osteoporotic Men & Women as adjuvant treatment,1-2 tabs daily. Tablet to be swallowed with a glass of water.* **Warnings:** *This is a food supplement. Food supplements should not be used as a substitute of any various diet.The specific recommended daily dose should not be exceeded.*

1. Bischoff-Ferrari JA et al. (2008). Effect of calcium supplementation on fracture risk: a double-blind Randomized ontrolled trial. American Journal of Clinical Nutrition. 87 (6), 1945-1951

C-VITAL
Vitamin C 1000mg

Composition: *Each effervescent tablet contains 1000mg Ascorbic acid (BP), Excipient q s 1 tablet*
Recommended Daily Dosage: *One effervescent tablet dissolved in glass of water.*
Warnings: *This is a food supplement. Food supplements should not be used as a substitute of any various diet. The specific recommended daily dosage should not be exceeded.*

Helps support your immune system with a great tasting flavour

The spirit of Alma-Ata

continued from page 4

What is the meaning of going back to Alma-Ata now? It leads to an enhancement of the provision of primary care which implies the reaffirmation of the role of family doctors and nurses. The growth of PHC and Family Medicine, which represents a major part, is of great importance, because the challenge for medicine in the third millennium is to achieve the right balance between modern technologies and interpersonal relations. Such a commitment implies rethinking the issue of humanization/dehumanization, with all its underlying physical, psychological, cultural and relational aspects. Family doctors are in a privileged position, because Family Medicine is the place where medical sciences merge with other disciplines, in particular sociology, economics, philosophy and jurisprudence. The Alma-Ata declaration that health is not merely the absence of disease renewed the meaning of the concept of care, transcending a restrictive view of care simply as treatment. A shift was made, which is characteristic for Family Medicine, from patient to person, from treatment to caregiving. As a fact, in Family Medicine the human being is viewed as a part in a network of relationships. Treatment thus becomes more of a social process, attention is given to circumstances, such as diseases affecting children, the elderly and women. Of course, these tasks are determined to a considerable extent by the health care system in which family doctors work and by the changing needs and demands of the patients. Family practice has always proved very good at adapting and responding to changing needs and demands of patients, much more than hospital doctors. Simply because we, as family doctors, are closer to the patients.

Gay considered the disease as the result of organic, human and environmental factors[2], a concept like the biopsychosocial model of Engel in his "holistic" model[3]. Efficiency as illustrated by Gay refers to the cost efficiency as a characteristic feature of well-developed family health care systems[2].

Again, if we want to promote health and wellbeing by applying health promotion and disease prevention strategies appropriately, we could use a comprehensive approach, that is often in contrast with the specialist approach in treating each problem separately. Throughout Europe, we are seeing many family doctors handling risk factors whilst promoting self-care, thus limiting the impact of patients' illnesses on their wellbeing, by taking into account the patients' personalities, families, daily life, physical and social surroundings, and, also, their backgrounds, cultural and religious beliefs.

This is why EURACT is stressing the Alma-Ata philosophy, promoting high levels of teaching and health promotion, and looking for mandatory specific training.

Society has changed over the years and there has been an increasing role for the patient as a determining factor in health care and its provision. We must now organize an approach to care which has to ensure a balanced use of technology and support systems in providing care, to implement a social model truly consistent with the human nature and its needs. Putting forward such a model entails a significantly different educational-training dimension, which would foster an increased interaction between healthcare providers and patients and between the different professionals involved in the treatment and care who intend to work for the good of the single person and the community.

Also here EURACT values were formed by the Alma-Ata Declaration, taking strong consideration of the community orientation. This is because family doctors have a responsibility for the community in which they work and must understand the potentials and limitations of the community.

As in all societies health care systems are being rationed and doctors involved in such initiatives, as well as in ethical and moral decisions, are in the best position to try and influence the health policy in the community. How? It could be by reconciling the health needs of individual patients and of the community, in balance with readily available resources.

To be able to do so, they need to learn in their undergraduate and vocational training the interrelationships between health and social care, the impact of poverty, ethnicity, inequalities, the structure of the health care system in which they live and in which they work[1]. How to learn this? With case-discussions, record reviews, visiting health and social care institutions and practice audits. This paper is, as all political documents, an indication, a way, to be integrated in each member states' reality. In fact, advocacy is a big point, helping the patient take an active part in the clinical process and working with the government and other authorities to maximise equitable distribution of services to all members of society.

References

1. EURACT Council. The Educational Agenda of General Practice/Family Medicine. Leuven, 2004.
2. Gay Bernard. What are the basic principles to define general practice. Presentation to Inaugural Meeting of European Society of General Practice/Family Medicine. Strasbourg, 1995.
3. Engel GL. The clinical application of the biopsychosocial model. *Am J Psychiatry* 1980;137(5):535-44.

Bibliography

1. Starfield B. Is Primary Care Essential. *The Lancet*. 1994; 344:1129-1132.
2. Starfield B. Primary care: balancing health needs, services and technology. Oxford: Oxford University Press, 1998.
3. The European Definition of General Practice/Family Medicine. WONCA Europe, London, 2002.
4. The General Practitioner in Europe: A statement by the working party appointed by the European Conference on the Teaching of General Practice. Leeuwenhorst, Netherlands 1974.
5. Olesen F, Dickinson J, Hjortdahl P. General Practice – time for a new definition *BMJ* 2000; 320:354-357.
6. Framework for Professional and Administrative Development of General Practice/Family Medicine in Europe. WHO Europe, Copenhagen, 1998.
7. Balint M. The Doctor, his Patient and the Illness. Pittman Medical, London, 1964.
8. Pereira Gray D. Forty-seven minutes a year for the patient. *British J Gen Pract* 1998; 437:1816-1817.
9. McWhinney Ian R. The importance of being different. *British J Gen Pract* 1996; 46:433-436.

Francesco Carelli is a General Practitioner and Professor of Family Medicine at the University of Milan. He is the Italian representative on EURACT's Council and Director of Communications and Chairman of the Basic Medical Education Committee within EURACT. EURACT is the European Academy of Teachers in General Practice. He is member of the RCGP and the General Medical Council (London), Trustee for International Academy of Educational Services and International Ambassador for the Association of Health Care Professionals. He is also a member of the Italian Journalists Council as well as Editorial Board member of scientific journals for General Practice including EJGP, IJM, NWLJP and LJPC. He is also author of numerous papers published internationally.