Issue 02/10

Newspaper post

TheSynapse

The Medical Professionals Network

Exclusive

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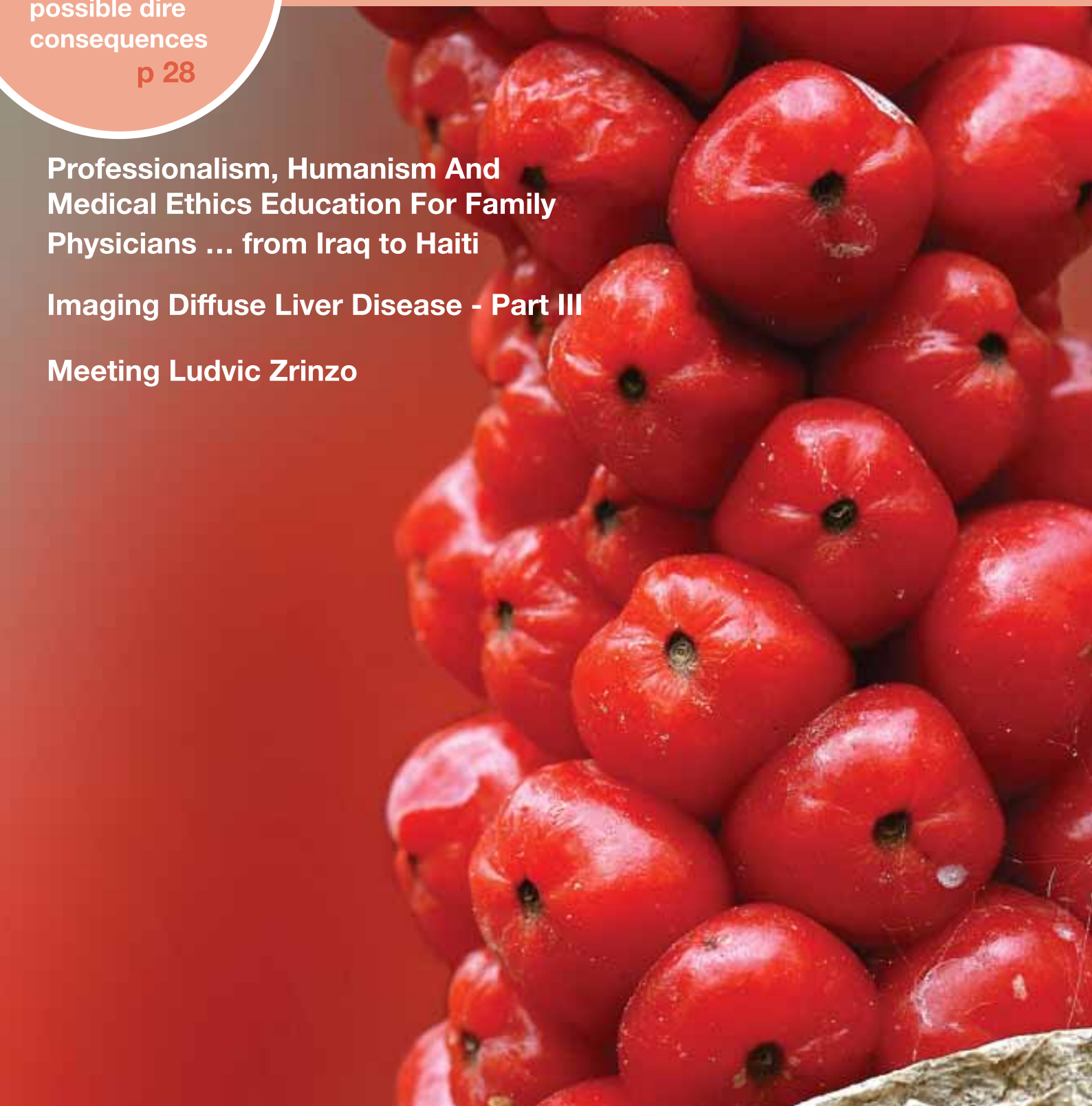

Professionalism, Humanism And Medical Ethics Education For Family Physicians ... from Iraq to Haiti

Imaging Diffuse Liver Disease - Part III

Meeting Ludvic Zrinzo

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Editor's word

As I was in the lobby of a hotel awaiting a colleague to discuss a preliminary agreement between her professional association and The Synapse, I came across an article which highlighted the use of Quantum Dots to tag DNA-repair Proteins. Apparently researchers have proposed that repair proteins efficiently scan the genome for errors by jumping like fleas between DNA molecules. They tagged two repair proteins, UvrA and UvrB, with quantum dots and watched while UvrA proteins randomly jumped from one DNA molecule to the next, holding on to one spot for about 7 seconds before hopping to another site. However when UvrA formed a complex with two UvrB molecules, the new complex slid along the DNA tightrope for as long as 40 seconds before detaching itself and jumping to another molecule. Obviously the relevance of these findings lie in the fact that in humans, approximately 10^7 cells divide per second with estimates suggesting that spontaneous mutations arise in about a third of those cells. The findings are available in *Molecular Cell* of last month.

Further research published last February in the *Journal of the American Chemical Society* details how capping quantum dots with mannose or galactosamine makes these quantum dots accumulate in the liver. This selective targeting could be used to deliver drugs to a specific organ, without causing systemic adverse reactions (which occur with existing drugs). To date, researchers still have not found an ideal way to target these dots to specific tissues or organs. These two different yet related examples highlight the many complimentary facets of medicine. Adding new platform technologies (to developing ones such as stem cell therapy and monoclonal cell therapy) to target disease is obviously further enhanced by a deeper knowledge of existing self-repairing mechanisms. It is only by using this binary system of research and development that we can develop better armamentarium to target specific diseases such as oncology. This is even more relevant in drug-resistant or refractory cases in selected subpopulations. A case in point is paediatric nongerminomatous malignant germ cell tumors.

It is indeed a point of personal contempt that even though we have been around for thousands of years (and taking into account selective sweeps) it is only recently that we have started to edge nearer to understanding basic principles of molecular biology, and to develop feasible and effective applications of quantum nanotechnology in medicine. Presumably this revolves around the fact that during the last decades funding in research and development (and locally we are not immune to this) has always been sorely lacking. But it would be grossly unfair to state that this depends solely on lack of funds. Sometimes it is a pandemic which is draining our earmarked research coffers, whilst other causes can also be an underestimated recession arising from various parts of the world such as America, Dubai or even Greece which eventually spreads like a drop of ink on blotting paper … and at times the culprit is simply a white elephant.

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

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Designer: - Jeff Galea

Printer - Europrint Ltd.

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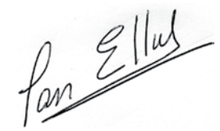
However, of one thing I am sure. This year will herald even more exciting discoveries … perhaps they will draw us nearer to developing the famous magic bullet technology in a feasible and cost-effective way spanning horizontally across all therapeutic classes ... who knows?



Ian C Ellul

Issue Guide

Contributors

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Hospital, Malta.

Dr Robert G Xuereb MD FRCP FASA FESC, Consultant Cardiologist and Senior Lecturer, is a clinical, non-invasive, and interventional cardiologist. He is the author of numerous publications in international peer-reviewed journals.

Dr. Samuel Aquilina MD graduated in July 2006 and has been a trainee in Paediatrics since October 2008. He is currently reading for a Masters in Community Child Health at the Institute of Child Health at University College London. The co-author of his article is Dr Thomas Attard.

Dr Nazan Karaoglu is a Family Medicine Specialist. She is currently working as an assistant professor in the Medical Education and Informatics Department of Selcuk University, Meram Faculty of Medicine, Konya, Turkey. The co-author of her article is Professor Francesco Carelli.

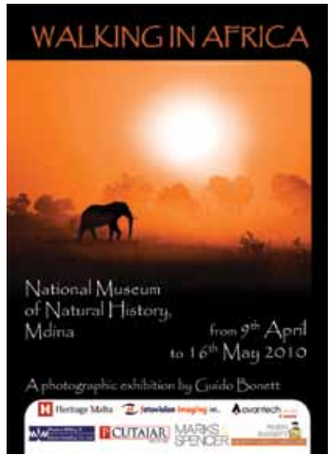
Professor Albert Cilia-Vincenti MD FRCPath was Pathology Director to the Winchester & Eastleigh Healthcare Trust and Pathology Chairman, Malta Health Service. He served as London University Lecturer and was Pathology Head, University of Malta. He maintains an interest in nutritional and natural medicine and longevity, and also in wine. He is founding committee member of *il-Qatra*.

Dr Tanya Melillo Fenech MD MSc is a Public Health Specialist and Head of the Infectious Disease Prevention and Control Unit. She is mainly involved in influenza surveillance, pandemic preparedness and response, Chemical, Biological, Radiological and Nuclear (CBRN) preparedness and vector borne disease.

Miran Spiteri is a 5th year Pharmacy student. This work is part of her project carried out for the partial fulfilment of the requirements of the course leading to the Degree of Bachelor of Pharmacy (Hons.). It was carried out under the supervision of Professor L. Azzopardi, Professor A. Serracino-Inglott and Dr. M. Zarb-Adami from the Department of Pharmacy.

Kristian Sant is a 5th year medical student. His future plans include enrollment in the Foundation Programme in Malta where he aims to gain expertise in a variety of medical and surgical fields. The co-author of his article is Dr Etienne Muscat.

Contents



The exhibition encapsulates Guido's photographic abilities and his meticulous approach towards documenting the beauty of wildlife and people on the African continent. The exhibits provide a whirlwind, yet distinctly breathtaking tour of his recent photographic safari across more than 5000 kilometres of road, spanning from Cape Town to Livingstone in Zambia.

For almost a month, Guido, together with an intrepid band of likeminded friends, endured the trucking and camping challenges which the vast expanse of Southern Africa had in store.

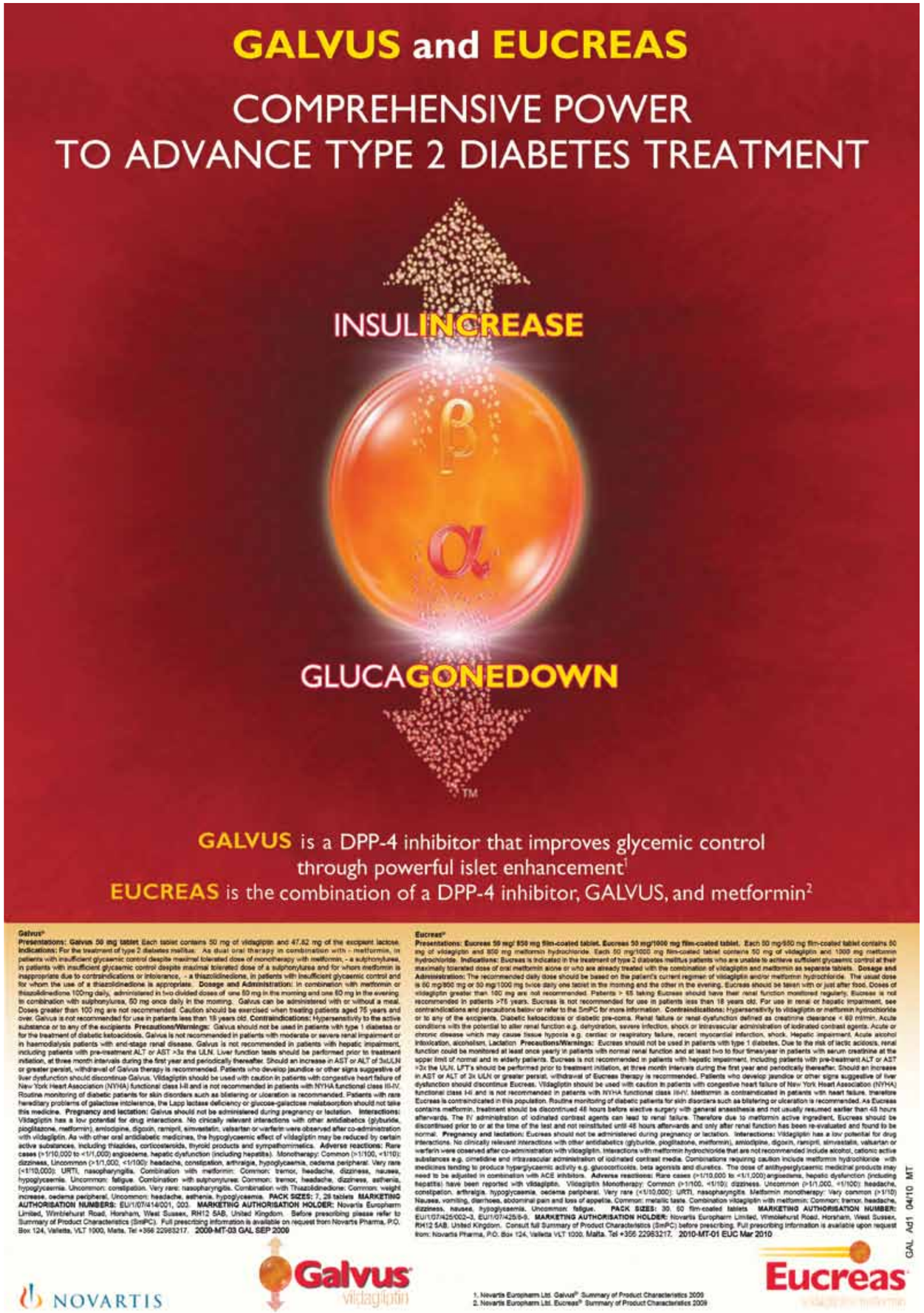
Worthy of mention are the visits to Cape Point national park, Namaqualand, Gariep River, Fish River Canyon, the great Sossusvlei sand dunes, Dead Vlei, Etosha, the Okavango Delta and Victoria Falls, as also the photographic encounters with the Himba in the Namib desert and San bushmen in the Kalahari. More than 6000 digital photographs later, Guido has the pleasure of sharing WALKING in AFRICA.

Front Page

Arum italicum (Italian Lords and Ladies; Cuckoo Pint)

Arum italicum thrives in moist and partially shaded conditions, and is commonly found in valleys and under walls. Its leaves and berries are poisonous if eaten. The starch from its tubers has been used to remove freckles. It has also been used to dress wounds, and as an antihelminthic and antitussive.

Photography: Guido Bonett ARPS AMPS
Reference: Lanfranco G. Hxejjex medicinali u ohrajn fil-gzejjer Maltin. Media Centre Print; Malta. 1993.



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Managing Pharmacist Vacancy
A vacancy has arisen for a full-time / reduced hours managing pharmacist to run a refurbished pharmacy in the South-Eastern region. The pharmacy does not have the POYC scheme as yet. The managing pharmacist is primarily expected to dedicate him/herself to the provision of a sterling service to patients. The chosen applicant should have a university degree in Pharmacy. Previous experience as a managing pharmacist will be considered an asset.
Benefits include:

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5. Sponsored local medical education events;
6. Ample parking space available;
7. The owner is a phamacist and thus locum coverage for emergency leave will be provided.

The vacancy is ideal for pharmacists residing in the Southern area who practise in the Central/ /Western/Northern areas of Malta, who wish to work nearer to their home. Especially mothers who wish to return to work on a reduced hour basis. Kindly contact by sms on 79060903 or send a CV to The Professional Services Centre, Guzi Cutajar Street, Dingli, DGL1201, referencing *Pharmacist Vacancy* on the envelope. Pharmacists interested in doing locums are also kindly requested to contact us on 79060903.

Clinic spaces available at St. Brigid's Centre, Gzira for the following specialities: General Surgeon, Paediatrician, Child Psychologist, Adult Psychologist, Dermatologist, Psychiatrist, Orthopaedic specialist & Family doctors interested in joining a group practice. Kindly contact or write an e-mail to drmartinborg@onvol.net

Visiting Rooms Available
Visiting rooms are available in a central location in **Burmarrad**. It is aimed that a centralised service is created for surrounding areas. General Practice, Paediatrician, Gynaecologist, Dermatologist, General Surgery, Orthopaedic Surgeon, Podiatrist, Nutritionist. For more details please enquire on 21582797 or 9984 5587. Clinics available at a newly refurbished pharmacy in **Mellieha**. Clinics are spacious and fully airconditioned with a large waiting room area as well as a reception service. Interested parties please contact Ms Dorianne Attard 23976000.

Da Vinci Hospital
The management of Da Vinci Hospital, B'Kara would like to announce that a consultation room space is available for use by any interested doctors, specialists and paramedical practitioners. If interested please call 21491200.

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Ophthalmologist available and interested to work in Malta Hospitals or clinics on short or long term basis, CV available on request. Please send an email, at: himaryuk@yahoo.co.uk

Aphasia and Psychiatric disturbances in Cerebrovascular accident patients

by Kristian Sant & Etienne Muscat

Aphasia is a condition in which there is a defect or loss of the power of expression by speech, writing, or signs, or a defect or loss of the power of comprehension of spoken or written language. 21-24% of patients admitted to hospital with acute stroke are aphasic shortly after their stroke and in the long-term it is likely that 10-18% of survivors are left with significant aphasia. Among these patients, a variety of neuropsychiatric symptoms arise as a complication of stroke but their diagnosis is often delayed by the presence of speech and language problems.

Aphasia is the considered to be the most important diagnostic symptom in predicting the location of a brain lesion. Prefrontal lesions are generally supposed to cause personality and emotional disorders, the most distinctive being disinhibition. Parietal lesions cause apraxia and subtle sensory disturbances. The occipital lobes are concerned with vision but evidence for location of specific types of psychovisual disturbance is often conflicting. Dementia in which there is slowing down of thought processes rather than memory loss, is considered to be subcortical. Brain stem lesions characteristically produce deep coma and localised neurological signs rather than mental symptoms but can also lead to confusional states or hallucinations. Mental disturbance is much more obvious if the damage is in the right hemisphere rather than in the left since a left-sided infarct leading to right-sided hemiparesis and loss of speech makes it difficult to detect certain deficits.

Most patients with stroke related aphasia improve mostly in the first 10 weeks and may keep improving till the 18th month. Speech and music therapy have been proven effective in recovery but improvement is dependent on a patient's decision to learn. A personalised multidisciplinary approach is essential for management of an aphasic patient and must include elements of education, support and communication skills conducted ideally by a speech and language pathologist, social worker and clinical psychologist. Involvement of family members and friends can further increase the efficacy of rehabilitation. Moreover, the use of bromocriptine as an adjuvant to traditional speech language therapies is associated with significant improvement in non-fluent aphasia. Also, dopamine and its agonists not only improve the dopaminergic stimulation dependent language functions (i.e. verbal latency and reading comprehension), but they also seem to improve the mood of patients. Stimulants such as amphetamines and amphetamine salts might also help recovery after stroke.

Aphasia and depression commonly coexist and develop as a consequence of stroke; moreover, having aphasia increases the risk of developing depression. Other neuropsychiatric conditions (e.g. dementia, anxiety disorders, and psychotic disorders) and symptomatic correlates (e.g. apathy or fatigue), may further obscure the diagnosis and the care of stroke patients. These conditions arise, in part, from the size and location of the lesion. There is evidence that depression is caused by both biological factors provoked by brain injury, associated with left anterior and basal ganglia lesions and lesions close to the frontal pole, and a secondary psychological response to the physical, cognitive, and social impairments produced by the stroke. 30-50% of stroke survivors suffer post-stroke depression with the same signs and symptoms as minor and major depressive disorders, characterized by lethargy, irritability, sleep disturbances, lowered self esteem and withdrawal. Depression can reduce motivation and worsen outcome. Initiation of somatic therapies such as antidepressants, stimulants or electroconvulsive therapy can contribute to symptomatic relief and help to ensure sufficient co-operation of the patient. Controlled studies have demonstrated that various classes of antidepressants are effective in treating post-stroke depression. Behavioural therapy such as cognitive behaviour therapy or other forms of talk therapy, especially interpersonal therapy can also help.

The discovery of specific neurotransmitter-producing areas and distribution pathways has suggested that a strategically situated infarct might produce a specific deficiency of that neurotransmitter. This might be a way in which stroke leads to depression. In brain injury, an excitotoxic effect takes place at the NMDA receptors resulting in an excessive inflow of calcium into the receptor nerve cell and a sequence of chemical changes killing the cell. One approach to treating acute stroke has therefore been to use drugs that counteract glutamic acid, and drugs that block NMDA receptors have been used in stroke treatment although they might themselves cause mental disturbances.

There is also a direct effect of stroke in producing fatigue. Post-stroke emotional problems including anxiety, panic attacks, flat affect, mania, apathy and psychosis can result from direct damage to emotional centres in the brain or from frustration and difficulty adapting to new limitations. Delusions are more often associated with lesions in the right hemisphere, posterior areas and left temporal lobe. Anxiety and nervousness are more frequent in the first year after a stroke but thereafter, tend to improve. Treatments for anxiety include psychotherapy and hypnotic-anxiolytic medication like benzodiazepines which might cause drowsiness as they act at the GABA-A receptor. Buspirone, by altering serotonergic transmission can reduce anxiety without causing drowsiness. Antipsychotic medication is useful but very paranoid patients might refuse it and side-effects of drowsiness and parkinsonism might cause major difficulties in post-stroke patients.

Studies show that communication problems of cerebrovascular accident patients due to aphasia affect the quality of life not only of patients but also of their carers. Failure to rehabilitate properly might be due to increased apathy after a stroke. In fact, 20% of stroke patients develop apathy and lack the motivation to return to mobility. Young patients are often intolerant of rehabilitation procedures that they cannot perceive as immediately leading to desired objectives. In conclusion patients' motivation and caregivers' patience are crucial in a quick and effective rehabilitation process.

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Interactions with concomitant use of quinolones antibacterials. **Adverse reactions: Common undesirable effects are:** Headache, dizziness, vertigo, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, transaminases increased, rash. **Rare undesirable effects are:** Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock), somnolence, asthma (including dyspnoea), gastritis, gastrointestinal haemorrhage, haematemesis, melaena, diarrhoea haemorrhagic, gastrointestinal ulcer (with or without bleeding or perforation), hepatitis, jaundice, liver disorder, urticaria, oedema. **Very rare undesirable effects are:** Thrombocytopenia, leukopenia, anaemia (including haemolytic anaemia and aplastic anaemia), agranulocytosis, angioneurotic oedema (including face oedema), disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, visual disturbance, vision blurred, diplopia, tinnitus, hearing impaired, palpitations, chest pain, cardiac failure, myocardial infarction, hypertension, vasculitis, pneumonitis, colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis, fulminant hepatitis, bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus, acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis. **Marketing Authorisation number:** MA 088/00303 **Marketing Authorisation Holder:** Novartis Pharmaceuticals UK Ltd., Frimley Business Park, Frimley, Camberely, Surrey GU16 7 SR, UK. 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NOVARTIS

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Professionalism, Humanism & Medical Ethics Education for Family Physicians ... from Iraq to Haiti

by Nazan Karaoglu & Francesco Carelli

Although we are in a time of progress and civilization, uncountable natural and man-made disasters are going on all over the world. We are unable to avoid terrorism, wars and violence and at times, like the recent Haiti disaster, feel that we are entrapped between national policies and medical ethics.

In 1978 the WHO in the Alma-Ata conference identified primary health-care as the key to achieving an acceptable level of health throughout the world. Besides the technical education of the family physician, political, ethical, and communicative competencies are very important for the multi-professional approach of a family physician. A successful humanitarian work depends on historical and ethical consciousness, knowledge of international humanitarian law and a culturally sensitive healthcare provision based on social and communicative competencies.

Being a kind, considerate and honourable professional practitioner is defined as possibly the most important element of being a good doctor.[1] Making the care of patients our first concern, protecting and promoting the health of patients and the public, treating patients as individuals, and respecting their dignity are the main responsibilities of family doctors.[2] The 1978 conference of the WHO in Alma-Ata identified "primary health care as the key to achieving an acceptable level of health throughout the world".[3]

Family physicians are in a unique and challenging position because they are often in the frontline of organizational and social change.[4] In this position family physicians suffer various tensions as they attempt to balance their own values with the expectations of their patients, the values adopted by organizations for which they work, and responsibilities of their profession.[5] Medical practice as an organized autonomic profession tries to update itself according to social and individual necessities.[2] Besides in special situations like natural disasters and terrorism the responsibility and the ethical challenges of family physicians naturally increase.

The impact of war on the health of a population is undoubtedly a cause of health inequalities.[6] The last decade has witnessed a large number of humanitarian emergencies of unprecedented proportions and variety.[7] Long-term exposure to such humanitarian emergencies causes serious psychological consequences in the wide spectrum of post-traumatic reactions both in patients and care givers.[8,9] Terrorism may have a severe impact on physicians' practices too.[10] Family doctors are likely to be the first point of care if a bioterrorism attack is suspected and they might need special training for this role.[11]

In a study in Lebanon the war and political tensions had a clear negative effect on interns in their attitude about life in general, their interactions with their patients, and their relationships with colleagues and staff.[12] Besides, according to a study in Iraqi it is suggested that physicians participated in human rights abuses through falsification of medico-legal reports on violence and death certificates.[13] Unfortunately this is the other side of the coin.
In complex emergencies, public health activities have been shown to promote peace, prevent violence, and reconcile enemies.[7] As Wong noted "as advocates of social justice, the medical profession has a duty to inform the public and to convince warmongers that war is unjust, damages life and health, creates misery and suffering, damages the environment, and wastes resources - resources that should be used to improve the health and welfare of people and to preserve our global environment".[14]

What should we do against the ethical challenges which we have in primary care? Apart from the technical education of the family doctor, education in political, ethical and communicative competencies are very important for the multi-professional approach of a family physician, as defined also in the European Definition of Family Medicine.[15]

Professionalism, humanism and medical ethics education have now resurfaced. Until recent years, these areas were generally neglected in education and in medical literature. Since we are healthcare professionals trained to help and care for others and following from the Codes and Oaths we have since Hippocrates and Maimonides, everything we did was by default ethical.[16] Obviously this is a wrong deduction.

As it is apparent in its definition, professionalism is a way of behaving in accordance with certain normative values and at least in theory, physicians could act in such a way as to fulfill all the expectations of professionalism without actually believing the values which underpin them.[17] Indeed daily expressions of professionalism mostly appear in physicians' offices and in the communities they serve, not in the academic corridors.[18]

Humanism is a way of being which comprises a set of deep-seated personal convictions and addresses the question of what it means to be human.[17,18] While humanism appeals to universal values, professionalism is rooted in the local traditions and thus the content of professionalism is narrower than that of humanism because it is the professional group which defines what the content and issues for professionalism will be.[19]

As mentioned before, specialty-specific training in ethics is especially important for family physicians and medical ethics education gained in medical school does not answer the need.[4]

As a conclusion, a family doctor (every one of us) should have the spirit of peace, humanity and ethics at the end of residency education.

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Constipation and Encopresis in Children

by Samuel Aquilina & Thomas Attard

Chronic constipation is defined as a decrease in frequency or the painful passage of bowel movements present for several weeks. Retentive encopresis is the term reserved for the involuntary and uncontrollable soiling that occurs in children with chronic constipation. Constipation is a relatively common paediatric complaint accounting for up to 3% of general paediatric outpatient visits and 25% of visits to a paediatric gastroenterologist.[1] Encopresis is also common, occurring in at least 1.5% of all children.

Despite its prevalence, most constipation in children tends to be functional or idiopathic. The natural history of functional constipation is that of an adaptive pattern of behaviour in a child who voluntarily withholds faeces followed by painful defecation. Retained stool eventually loses moisture to become harder and thus exacerbates the pain and difficulty with stooling. Eventually, the dilated distal colon is rendered mechanically ineffective to expel even stool of normal consistency. Since encopresis evolves through longstanding stool retention the dilated rectal vault becomes relatively insensitive to the presence of stool which is an essential prelude to conscious defecation. Rectal impaction with stool will compromise the functional integrity of the anal sphincter, and the process is further exacerbated through the intermittent attempts at treatment with laxatives leading to spurious diarrhoea. Withholding patterns usually follow changes in diet, toilet training, travel, viral illnesses, and obstacles to the use of toilet facilities outside the home including unsanitary conditions or lack of privacy.

A thorough history and physical examination are critical in the assessment of the child with constipation, and in most cases is sufficient to allow the doctor to establish the diagnosis of functional constipation. An appreciation of the age-dependent variability in stool frequency is essential to define the degree of severity of the process (Table 1). From this table, one can note that breast-fed babies pass more stools than formula-fed babies. No data is given for 3-6 months old babies, however extrapolatingly it also depends on whether they are breast- or bottle- fed. Salient historic points include background other gastrointestinal symptoms and growth parameters, age at, and difficulty with, toilet training, current diet, and previous episodes of constipation and perianal fissures. Multiple, organic and behavioural – emotional precipitants have to be borne in mind and, depending on the index of suspicion, ruled out (Table 2). Withholding behaviours of children include stiffening of buttocks or legs, wriggling, rising on toes, and assuming unusual postures and avoidant behaviour. The physical examination should include a rectal exam; important components of this part of the assessment include inspection for sacral dimple and in most cases digital examination of the rectum to determine perianal sensation, tone, anal reflex, amount and consistency of stool, while checking externally for fissures, skin tags and perianal erythema.

The management of the child with functional constipation includes reassurance and education of the patient and parents, initial disimpaction of retained stool followed by maintenance therapy with long-term laxatives and behaviour modification.

Education – It is important that the pathophysiologic process involving stool retention, be explained in understandable form to the parents. Encopresis, when present usually entails an adversarial interaction between caregivers and the patient, the latter being accused of voluntary soiling which is, most often not the case. Other aspects of treatment include an explanation of the chronicity of the condition along with long term aspects of care.

Disimpaction – This is necessary before initiation of maintenance therapy. It can be achieved preferably with oral medication. In infants, rectal disimpaction can be achieved with glycerin suppositories. In children, a range of medications exist such as mineral oil, polyethylene glycol, lactulose, sorbitol, senna, magnesium hydroxide and citrate; including enemas. In refractory or severe cases, inpatient admission with a Nasogastric tube placement and polyethylene glycol drip may be necessary.

Maintenance therapy – the aim here is to prevent recurrence. Dietary changes, namely increase in insoluble fibre, can be implemented but are rarely sufficient. Although recent literature has questioned the validity of chronic non-stimulant (bulk-forming) laxative use,[2] chronic administration of a non-stimulant laxative appears to be the standard of care. Given the slow evolution of chronic constipation, and the risk of developing a relatively atonic colon, patients are usually treated with non-stimulant laxatives on a long-term basis, sometimes for years.

Behavioural modification – The use of medications in combination with behavioural management can decrease the time to remission in children. Regular unhurried toilet

Continues on page 30

Product Information. **alli** 60 mg hard capsules (orlistat) **Indication:** Weight loss in adults BMI ≥28 **Dosage:** Adults (18 or over) One capsule with each of three main meals. Max. 3 caps/day for up to 6 months. Use with mildly hypocaloric, lower-fat diet. If no weight loss within 12 weeks, refer to doctor or pharmacist. Diet and exercise should start prior to treatment. **Contraindications:** Hypersensitivity to ingredients; concurrent treatment with oral anticoagulants or ciclosporin; chronic malabsorption syndrome; cholestasis; pregnancy; breast-feeding. **Special warnings and precautions:** Talk to doctor before starting to take alli if taking amiodarone, a medicine for diabetes, epilepsy or hypothyroidism, or if patient has kidney disease. If taking a medicine for hypertension or hypercholesterolaemia, talk to doctor or pharmacist when taking alli. Risk of gastrointestinal (GI) symptoms increases with fat consumption. Take multivitamin at bedtime. See doctor if rectal bleeding occurs. Oral contraceptive efficacy may be reduced if severe diarrhoea occurs; use additional contraception. **Drug interactions:** Ciclosporin; oral anticoagulants; levothyroxine; antiepileptic medication; oral contraception; fat soluble vitamins; acarbose; amiodarone. **Pregnancy and lactation:** Do not use during pregnancy or lactation. **Side effects:** See SPC for full details. Predominantly GI e.g. oily stools, urgency; usually mild and transient, risk reduced by low fat consumption. Diverticulitis; pancreatitis; mild rectal bleeding; hepatitis; cholelithiasis; abnormal liver enzymes; anxiety; hypersensitivity reactions including anaphylaxis, bronchospasm, angioedema, pruritus, rash, and urticaria; bullous eruption. **Legal category:** Non-prescription. Marketing Authorisation Holder: Glaxo Group Limited, Greenford, Middlesex, UB6 0NN. **MA Number:** EU/0/09/0601007 - 010. Pack size: 84s. **Last revised:** March 2010.

COMPETITION ANSWERS – ISSUE 1/10

An 8 year old boy from Balzan presented with a 4 week history of intermittent fever. On examination, he had anaemia and had hepatosplenomegaly. A splenic aspirate revealed numerous microorganisms within macrophages.

Photo Credit - Prof Michele Maroli
Istituto Superiore di Sanita, Roma

What is the name of his disease? Systemic leishmaniasis. Synonyms: Visceral leishmaniasis; Kala-Azar.
What is the name of the most prevalent insect vector in the Maltese islands? *Phlebotomus perniciosus*.
What is the name of the causative parasite in the Maltese islands? *Leishmania infantum*.
What is the name of the parasite observed microscopically within the macrophages? LDB's = *Leishman-Donovan Bodies*.
What constitutes the most important reservoir of infection? Infected dogs.

The term "leishmaniasis" refers to a group of zoonoses caused by a protozoan species in the genus Leishmania. Some 20 species infect man. The disease is transferred to humans from a reservoir vertebrate species by the bite of an infected sandfly. It is widely prevalent in many tropical and subtropical regions of both the Old and New World. The exact clinical manifestations, vector species, causative protozoan and reservoir of infection vary according to the geographical location in which it is acquired. Systemic, mucocutaneous and cutaneous forms of the disease occur.
Many misconceptions abound regarding the epidemiology of the disease in the Maltese islands. Cutaneous leishmaniasis, for example, is more commonly but not exclusively acquired in Gozo. *Phlebotomus perniciosus* is by far the most common vector species, and not *P. papatasi* which was last recorded in Malta in 1932.[1] In the Maltese islands, both systemic and cutaneous disease are caused by the same, and not different, species of Leishmania which is *L. infantum* and not *L. donovani*. And although dogs are currently thought to be the most important local reservoir of infection, cats have also recently been found to be commonly infected [2] and may play a more important role in the transmission of the disease than previously thought.

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Unfortunately none of the answers received were correct. The editorial board has therefore decided that the vouchers which were not won will be added to this issue's competition.

THIS MONTH'S CHALLENGE €100 book vouchers to be won

A 54 year old farmer developed high fever, chills, aches and pains, severe headache and photophobia, followed 4 days later by a rash. On examination, she looked unwell, was febrile, and had a maculopapular rash (Figure 1) which involved the palms. Closer inspection revealed a healing necrotic ulcer on the skin of her back (Figure 2)

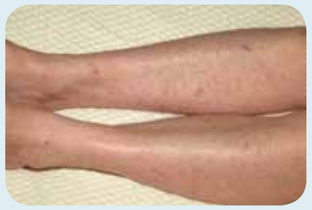

Figure 1

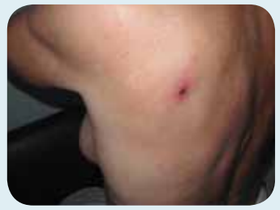

Figure 2

1. What is the name of her disease?_____
2. By what other name is it called? _____
3. What name is given to the ulcerated lesion on her skin?_____
4. What is the name of the causative microorganism?_____
5. How is it transmitted?_____

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All submission will participate in a draw. The first correct answer to be drawn will win a €60 book voucher from BDL and the runner up will win a €40 book voucher from BDL. You have up to the 15th May 2010 to submit your answers.

Update on H1N1 Virus

by Tanya Melillo Fenech

Worldwide Situation
Although the pandemic influenza virus continues to be the predominant circulating influenza virus worldwide, circulation of seasonal influenza B viruses continue to increase and spread across Asia, parts of Eastern Europe, and Eastern Africa.

The overall pandemic influenza transmission continues to decline in Europe, North and South America, Southern Hemisphere, North Africa and Asia. Countries still reporting active influenza transmission include West Africa and parts of Southeast Asia with Thailand showing the most activity. Approximately half of all provinces in Thailand reported that more than 10% of all outpatients were seeking care for influenza like illness (ILI) and approximately 25% of all patients with ILI tested positive for influenza (currently the percentage for Europe is under 5%).

European Situation
For most countries in the European region, the pandemic influenza activity is considered to be reaching the end. Most experienced an early start to the influenza season (September/October) and the winter activity peaked earlier than in the past years (December as compared to February/March). In 19 of 22 countries reporting five or more years of influenza data, the peak clinical consultation rates that were observed during the 2009/2010 pandemic season did not exceed peak clinical consultation rates observed during the previous years. However in several countries, clinical consultation rates did exceed recent historical peaks within some younger age groups. 49 out of the 53 European countries reported laboratory-confirmed cases, the large majority of which occurred without complications. 4573 laboratory-confirmed deaths associated with the pandemic (H1N1) influenza virus have been reported to WHO/Europe. However this is an underestimation of the actual number of deaths associated with the pandemic H1N1 virus infections. 99.74% of influenza virus detections during 2009 were Influenza A (H1N1). All the pandemic (H1N1) 2009 viruses analysed antigenically or genetically were similar to the vaccine strain and the majority was sensitive to both oseltamivir and zanamivir. Presently less than 5% of influenza-like illness seen by sentinel doctors are positive for H1N1.The number of reported Specific Acute Respiratory Infective cases has also continued to decline.

Local Situation
The last positive H1N1 confirmed case was on the 19th of February and the last Influenza A confirmed case was on the 20th of February. Since then all swabs have been negative. Antiviral dispensing has been decreasing exponentially since the end of January. 91,922 persons up to the 16th of March have been vaccinated. The rate of influenza-like illness during week 9 was around 73/1000 consultations, a slight increase from week 8 which was 58/1000 consultations.

Prior infection with classical swine H1N1 influenza viruses is associated with protective immunity to the 2009 pandemic H1N1 virus
A study done in USA and published in Influenza and other respiratory viruses last March on experimental mice, showed that induced immunity to the 1918-derived H1N1 seasonal influenza virus and the 1976 swine influenza virus, offered a degree of protection against the 2009 pandemic virus. The implications of these findings add to the accumulating data that is suggesting that reason for the partial protection of older persons against the 2009 pandemic.

Morbid Obesity: a risk of influenza-related complications
A case-control design used to compare cases of hospitalizations and deaths from the 2009 Influenza H1N1 pandemic occurring between April and July 2009 in the US suggested that persons who were morbidly obese (BMI≥40 kg/m^2) - even if they did not have chronic medical conditions recognized by the Advisory Committee on Immunization Practices as increasing the risk of influenza related complications - had an increased risk of hospitalization and potential death. These complications could be prevented with early antiviral treatment and vaccination.

Pandemic H1N1 mutation in India resembles Dutch findings
Researchers from India's National Institute of Virology announced this week that they detected a small mutation in the polymerase 2 (PB2) gene in the pandemic H1N1 virus in samples from three patients, the same change that surfaced in two Dutch patients last September. The Dutch researchers found the E627K mutation in the basic polymerase 2 (PB2) proteins in samples from two patients who had links to an island in northern Holland.
The E627K mutation in PB2 had previously been linked to increased replication and possible virulence changes in other influenza A viruses. Though the mutation has been rarely seen in avian-derived viruses, it had been associated with fatal H5N1 cases and H7N7 infections in humans. The clinical and epidemiological significance of the mutation is unclear and the experimental infection of ferrets with the H1N1 virus containing the mutation did not suggest increased shedding, virulence, or transmissibility.

Healing & Disease Reversal – Part IV

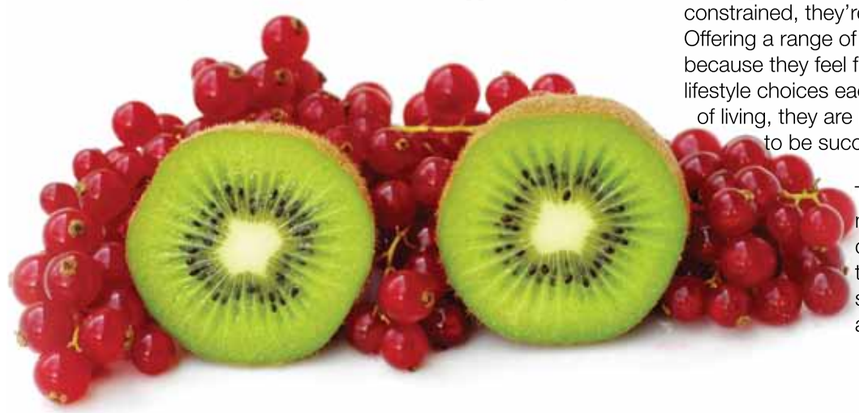
by Albert Cilia-Vincenti

This series explores Dean Ornish's 30-year research experience into healing and disease reversal by dietary and lifestyle changes. He is a California University Professor of Medicine in San Francisco. This instalment begins to explain why his programme works, whilst others prove to be unsustainable.

Dean Ornish claims that when people make the diet and lifestyle changes recommended in his programme, most of them find that they feel so much better so quickly that it reframes the reason for changing one's habits from fear of dying to joy of living. Joy and love are powerful sustainable motivators, but fear and deprivation are not.

Ornish contends that depending on how much you move in a healthy direction along his programme's range, you're likely to look better, feel better, lose weight and gain health. People have different needs, goals and preferences. What matters most is one's overall eating and living habits. One may indulge in food one day and eat more healthily the next. One can be a couch potato one day and exercise a little more the next. Consistency is more important than duration. This way one is less likely to feel restricted. In his view, people who eat most healthy are those who allow themselves some indulgencies.

If one is trying to reverse heart disease or prevent cancer recurrence, one may need bigger changes in diet and lifestyle than someone who just wants to lower his/her cholesterol level a few points or lose a few kilograms. If one has a strong family history, or if genetic testing shows one to be at higher risk, this can be a powerful motivator to make bigger dietary and lifestyle changes than one might otherwise make. It may also be possible to tailor drug therapy more effectively.
Many people have hypercholesterolaemia. You may initially advise them to follow a diet. For some, that's sufficient to lower their cholesterol adequately, but not for most. Then you usually prescribe cholesterol-lowering drugs, in many instances for the rest of their life. In Ornish's experience, most people can make progressively bigger dietary and lifestyle changes to achieve their goals, often without medication. How much people want to change is up to them. If they don't have a serious illness, such as coronary heart disease, it usually doesn't matter if they indulge themselves occasionally but, if they do have heart disease, even a single meal high in saturated fat may increase their risk of chest pain or even a heart attack. Even more than feeling healthy, most people want to feel free and in control. Telling people to "eat this and don't eat that" or "don't smoke" don't work, at least not for long, because human nature being what it is, they would want to do the opposite. Nobody wants to feel controlled or treated like a child. People need to feel empowered and in control, so that they can feel free to make healthy choices that are sustainable. They need to understand the reasons for eating this way, which is better than telling them "because I said so". If they go on a diet and lifestyle programme and feel constrained, they're likely to go off it sooner or later. Offering a range of choices is much more effective, because they feel free. If they see their food and lifestyle choices each day as part of a range, as a way of living, they are more likely to feel empowered and to be successful.



The language of behavioural modifications (like "cheating on a diet") often has a moralistic quality to it that turns people off. It's a small step away from thinking of foods as 'good' or 'bad' to seeing oneself

Continues on page 20

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Imaging Diffuse Liver Disease – Part III

by Pierre Vassallo

Vascular Disorders
Vascular stasis, hypercoagulability states and endothelial disruption (Virchow's triad) are known to be main mechanisms that cause thrombosis. Portal venous stasis caused by cirrhosis, hepatocellular carcinoma or pancreatic carcinoma may lead to portal venous thrombosis. Sepsis, direct trauma, inflammatory bowel disease and phlebitis all lead to endothelial damage that may result in portal venous thrombosis. Portal venous thrombosis is usually a transient condition, however if it involves the smaller intrahepatic branches revascularisation will not occur. When it persists, cavernous transformation of the porta hepatis occurs with the formation of numerous collateral venous channels that replace the main portal vein. CT will show both thrombosis of the portal vein and the sponge-like conglomerate of veins replacing it in the porta hepatis (Figure 1). It may also demonstrate the cause of the portal vein thrombosis.

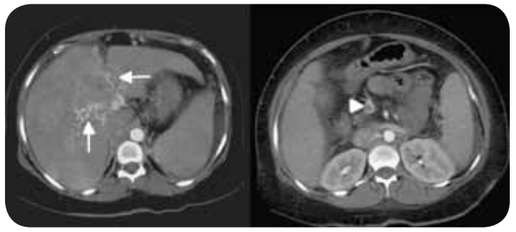

Figure 1
Cavernous transformation of the portal vein due to pancreatic cancer. Collateral veins (arrows) are seen filling the intrahepatic portion of the main portal veins. Thrombus in the extrahepatic portal vein (arrowhead).

Budd-Chiari syndrome results from occlusion of the hepatic veins and is classified into 3 types: Type 1 involves occlusion of the inferior vena cava, in type 2 there is occlusion of the major hepatic veins while in type 3 veno-occlusive disease of the liver or progressive thrombotic occlusion of small centrilobular veins is present. Stasis in the hepatic veins or IVC may result from external compression by a hepatic or retroperitoneal tumour or due to increased intraluminal pressure by congestive heart failure, constrictive pericarditis or a right atrial myxoma. CT can confirm hepatic venous or IVC thrombosis and can help identify the cause (Figure 2).

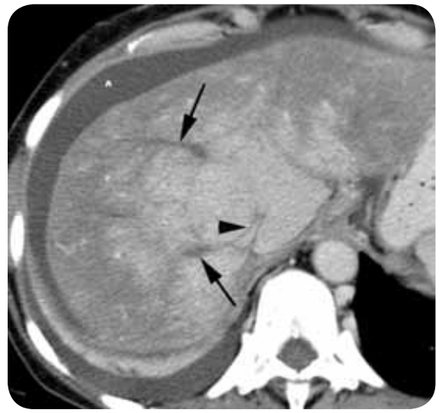

Figure 2
Budd-Chiari syndrome on CT: Portal phase CT showing diminished perfusion of the peripheral portions of the liver with increased central perfusion, thrombosed hepatic vein (arrows), a compressed IVC (arrowhead) and ascites (A).

Congestive heart failure results in stasis and increased pressure in the hepatic veins with hepatic congestion that if persistent for a long time will lead to hepatocyte necrosis, fibrosis and micronodular cirrhosis. In such cases, CT will demonstrate hepatic venous widening and evidence of cirrhosis.

Hepatic arterial occlusion is rare and is more frequently seen in transplant livers due to direct trauma. It is otherwise the result of embolic disease. The hepatic artery contributes only 25% of the liver's blood supply and if occluded does not grossly disrupt liver function. Metastases and primary liver tumours have been noted to receive most of their blood supply from the hepatic artery and chemo-embolisation of the hepatic artery is one of the treatment methods used to control tumour growth. Occlusion of the hepatic arteries, therapeutic or otherwise, is readily assessed by CT.

Significant liver infarction only occurs when both hepatic arterial and portal venous occlusion occur. Such situations include acute shock, trauma and hypercoagulability, as well as preeclampsia or HELLP (hemolytic anemia, elevated liver enzymes, low platelets) syndrome and as a vascular complication after liver

transplantation. CT will show the zone of infarction as a wedge shaped area of low density that follows the segmental vascular anatomy of the liver.

Inflammatory diseases of the liver
Viral hepatitis results in cellular alterations with varying degrees of periportal hepatocellular necrosis, Kupffer cell mobilization, and portal infiltration with plasma cells depending on the underlying infectious, toxic, or autoimmune cause. These inflammatory entities can be self-limiting, progress to segmental scarring, or end in an overall cirrhotic state. The acute variant of hepatitis lasts less than 6 months; chronic hepatitis represents any inflammatory condition of the hepatic parenchyma that does not show signs of regression for periods longer than 6 months.

CT of acute and fulminant courses of hepatitis shows generalized hepatomegaly combined with peripheral edema. Furthermore, nonenhanced CT can show heterogeneous attenuation patterns. The overall hepatic parenchymal attenuation is usually equal to or less than that of the spleen. Contrast-enhanced CT can demonstrate irregular perfusion with heterogeneous regions of diminished attenuation (Figure 3).

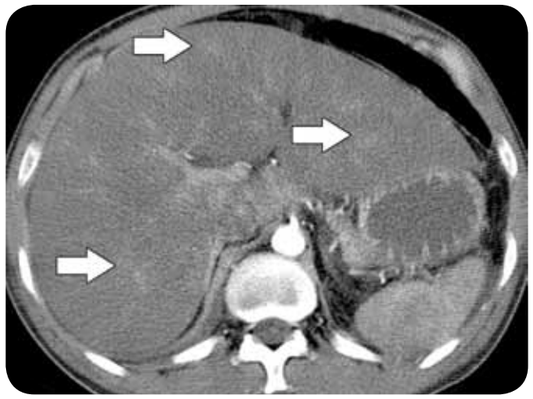

Figure 3
Acute viral hepatitis in a 39-year-old man: Arterial phase image shows heterogeneous enhancement (arrows) of the edematous enlarged liver.

Conclusion
The aim of this article was to demonstrate the prominent role of CT for the diagnosis of diffuse liver disease primarily due its excellent morphologic visualization capabilities.

Continues from page 17

as a 'good person' or a 'bad person' if you eat them. However, although we often project moral qualities onto it, food is just food. In the short term, one might be pressured into changing his/her diet, but sooner or later, one will rebel. Ornish's programme is therefore not trying to get people to do anything, but is only sharing information that they can use to make informed and intelligent choices.

How one eats is as important as what one eats. If a person is concentrating on television, reading or having a heated conversation while eating, he/she can go through an entire meal without tasting the food – having all the calories and none of the pleasure. On the other hand if that person concentrates on what he/she is eating, smaller food portions can be exquisitely satisfying. A calorie is a calorie in terms of its effect on one's weight, but not in terms of how much pleasure it provides. Paying attention to what one is eating will also make one notice how different foods affect him/her, and which ones affect negatively his/her general well-being.

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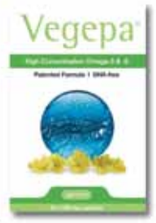

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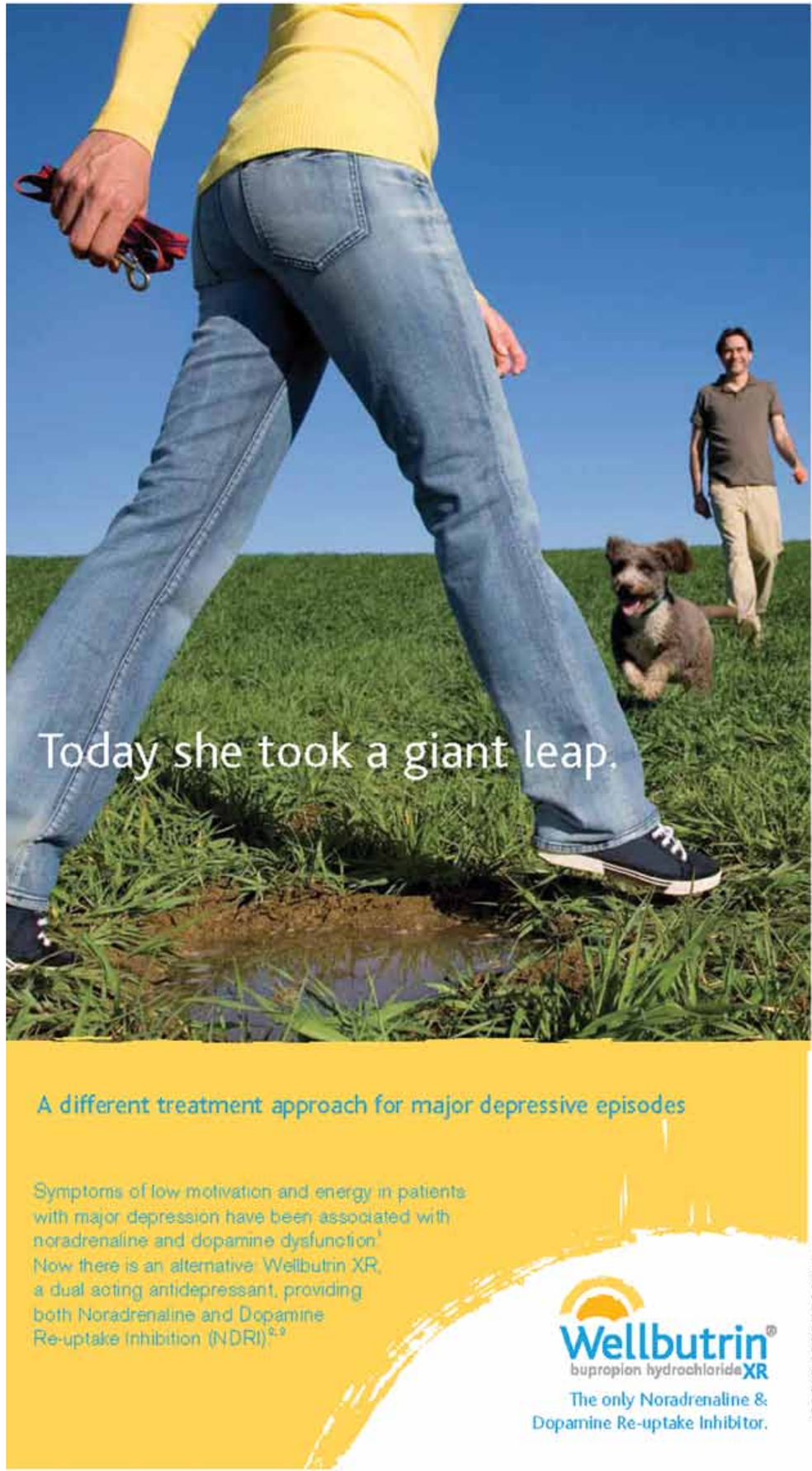

Bupropion XR Tablet (Wellbutrin XR') is a once daily medication for the treatment of depression. It should be distinguished from bupropion sustained-release tablets which are also available in Europe as:

- Wellbutrin SR - a twice daily medication for the treatment of depression.
- Zyban - a twice daily medication used as an aid to smoking cessation.

Wellbutrin XR', Wellbutrin SR and Zyban all contain the same active ingredient (bupropion hydrochloride) and should not be used together. Bupropion XR tablet should be swallowed whole and not crushed or chewed. The maximum dose of bupropion extened-release tablet should not be exceeded.

WELLBUTRIN XR ABRIDGED PRESCRIBING INFORMATION: Please refer to full Summary of Product Characteristics (SPC) before prescribing **TRADE NAME:** WELLBUTRIN XR **ACTIVE INGREDIENT:** Bupropion Hydrochloride 150mg and 300mg. **PHARMACEUTICAL FORM:** Modified release tablet **MAJOR INDICATIONS FOR USE:** WELLBUTRIN XR is indicated for the treatment of major depressive episodes **DOSAGE AND METHOD OF USE:** WELLBUTRIN XR tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse events including seizures; can be taken with or without food. Use in Adults: The recommended starting dose is 150mg once daily; if no improvement is seen after 4 weeks the dose may be increased to 300mg once daily. There should be an interval of at least 24 hours between successive doses. As with all antidepressants the full effect of WELLBUTRIN XR may not be evident until after several weeks of treatment; patients should be treated for a period of at least 6 months to ensure that they are free of symptoms. Insomnia is a very common but transient adverse event which may be reduced by avoiding dosing at bedtime. Use in Children and Adolescents: WELLBUTRIN XR is not indicated for use in children or adolescents aged less than 18 years. Use in Elderly Patients: Same as adults but with greater sensitivity in some elderly individuals. Use in hepatic and renal impairment: The recommended dose in these patients is 150mg once a day. Discontinuing therapy: Although no discontinuation reactions were observed during clinical trials with WELLBUTRIN XR, they cannot be excluded and a tapering off period may be considered. Overdose: In addition to those events reported as Undesirable Effects, overdose has resulted in symptoms including drowsiness, loss of consciousness and/or ECG changes such as conduction disturbances, arrythmias and tachycardia; deaths have been reported, rarely even with large overdoses. **CONTRAINDICATIONS:** Hypersensitivity to bupropion or any of the excipients; co-administration with other medicinal products containing bupropion as the incidence of seizures is dose-dependant; current seizure disorder or history of seizures, known CNS tumor, withdrawal from alcohol or any medicinal product known to be associated with the risk of seizures on withdrawal, severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **PRECAUTIONS:** Do not exceed the recommended dose of WELLBUTRIN XR especially in patients who have predisposing factors for seizures since the risk of seizures is dose-related. WELLBUTRIN XR is not recommended and should be discontinued in patients who experience a seizure during treatment. Careful monitoring should be carried out during the first weeks of treatment, during dose changes and in patients who have history of suicide-related events prior to treatment, close supervision should accompany drug therapy in particular those at high risk especially in early treatment and following dose changes. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medicinal product, in patients who experience the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. There is limited data on the use of bupropion in combination with mood stabilisers and ECT; WELLBUTRIN XR should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Even though bupropion was well tolerated in studies for smoking cessation in patients with ischaemic heart disease, there is limited clinical experience of its use to treat such patients with depression: therefore care should be exercised if it is used in these patients. Monitor blood pressure especially in patients with pre-existing hypertension; consider discontinuation if a clinically significant increase in blood pressure is observed. Use with caution in patients with hepatic and renal impairment. **DRUG INTERACTIONS:** Concomitant use with MAOI's is contraindicated, the dose of medicinal products which are metabolised by the CYP2D6 pathway like certain antidepressants, anti-psychotics, beta-blockers, SSRI's and Type 1C antiarrhythmics, should be reduced when given concomitantly with WELLBUTRIN XR; caution should be exercised when using medicinal products that may affect the CYP2B6 isoenzyme like cyclophosphamide and ticlopidine, those known to induce metabolism e.g. carbamazepine, phenytoin, ritonavir or inhibit metabolism e.g. valproate; caution also advised when Wellbutrin XR is administered to patients on levodopa or amantidine, alcohol and nicotine transdermal system. **ADVERSE EVENTS:** Very Common: Insomnia, headache, dry mouth, gastrointestinal disturbance including nausea and vomiting; Common: Hypersensitivity reactions such as urticaria, anorexia, agitation, anxiety, tremor, dizziness, taste disorders, visual disturbance, tinnitus, increased blood pressure (sometimes severe); flushing, abdominal pain, constipation, rash, pruritus, sweating, fever, chest pain and asthenia. Not known: suicidal ideation and suicidal behaviour (see Precautions). Refer to the SPC for a full list of adverse events. **PREGNANCY AND LACTATION:** Pregnancy: The safety of WELLBUTRIN XR for use in human pregnancy has not been established. Lactation: As bupropion and its metabolites are excreted in breast milk mothers are advised not to breast feed while taking WELLBUTRIN XR. **ABILITY TO DRIVE AND USE MACHINES:** Caution should be exercised until there is certainty that WELLBUTRIN XR does not adversely affect performance. **PRESENTATIONS: Wellbutrin XR 150mg and 300mg x 30 tablets LEGAL CATEGORY:** POM **MARKETING AUTHORISATION HOLDER:** TABLETS: Glaxo Group Limited, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, UK **MARKETING AUTHORISATION NUMBER:** MA 302/00101/03 **Further information and full prescribing information GlaxoSmithKline Malta Tel: 21 238 131 Date of preparation:** October 2006

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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, - and 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 as 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 ≤5 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 such patient and adjusted at 4 week intervals up to 80 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 at 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 disease influences the 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 hypercholesterolaemia 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 characterised 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 cytochrome P450 3A4 inhibitors (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. *Hydroxylated inhibitors:* Atorvastatin and its metabolites are substrates of P-glycoprotein. P-glycoprotein inhibitors (e.g. ciclosporin) 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 substances of this (unknown 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 same 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. **Hepatobiliary disorders:** *Rare:* Hepatitis, cholestatic jaundice. **Ear and labyrinth disorders:** *Uncommon:* Tinnitus. **Skin and subcutaneous tissue disorders:** *Common:* Rash, pruritus. *Uncommon:* Urticaria. *Very rare:* Angioedema, bullous eruptions (including erythema multiforme, Steven-Johnsons syndrome and toxic epidermal necrolysis). **Musculoskeletal disorders:** *Common:* Myalgia, arthralgia, arthritis. *Uncommon:* Myopathy, 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.

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An English-Maltese Dictionary of Medical and Pharmaceutical terms

by Miran Spiteri, Anthony Serracino-Inglott, Maurice Zarb-Adami, Lilian M. Azzopardi

An English-Maltese dictionary of medical and pharmaceutical terms is being made available for all those who need a quick reference to assist them in translating medical and pharmaceutical documents. This task is undertaken by pharmacy students (carried out under the supervision of academics) during the course of Pharmacy at the University of Malta.

Maltese has been a working language of EU institutions since the EU Commission recognised it as one of the twenty-three official languages of the European Union. In fact, the European Medicines Agency (EMEA) determined that 'certain documents for medicinal products authorised by the centralised system have to be translated into Maltese'.[1] Medical translators are experiencing difficulty in not having easily available Maltese equivalents for many of the English medical terms used in the documents to be translated. This is resulting in having non-standardised medical and pharmaceutical Maltese terms. An English-Maltese dictionary of medical and pharmaceutical terms thus contributes towards establishing such terms.

The Department of Pharmacy of the University of Malta has recognised this fact and in 2007, Eliza Camilleri, under the supervision of Professor Anthony Serracino-Inglott, compiled the terms from 'A' to 'E'. This work was disseminated in electronic format. In the current project, terms from letters 'F' to 'K' were translated and validation of the Maltese terms with an established linguist, laymen and healthcare professionals has been undertaken. The compilation of terms A-K, is being made available online and as a book.

The process of this dictionary's compilation consisted mainly of two phases. The first phase involved the collection of terms which had already been successfully translated and adapted into the Maltese language: this was done by gathering medical and pharmaceutical entries from the Medicine's Authority's 'Glossary of Terms'[2] and from the dictionary suggested by EMEA, the 'English to Maltese Dictionary' by Professor Joseph Aquilina.[3] The second phase involved the actual translations of medical and pharmaceutical terms which had not yet been translated into the Maltese language. Such terms were extracted from Mosby's Medical Dictionary[4] and translated in accordance with Medicines Authority's requirements and EMEA guidelines.[1] These new Maltese equivalents for English medical terms were then discussed with the linguist, in order to review the grammatical and linguistic issues. During this phase, the following three guidelines were followed:

1) Colloquial Maltese terms that are known to the majority of the Maltese population must be used. This is of vital importance since the translated documents must be clearly understood by the general Maltese public.

2) Generic and trade names should not be translated. The same applies for chemical names, excipients and names of enzymes. There is no need to use italics for these terms.

3) Prior to translating, a good understanding of the text is required since it is impossible to produce a good translation of a text unless this is fully understood. Literal translations must not be carried out since the intended message may be altered.

To enhance the quality of the dictionary, feedback on the newly translated terms was obtained from the target users (laymen and healthcare professionals) during the compilation process. This gave the possibility to consider the users' feedback for implementation prior to having the final version of the dictionary published, a process referred to as 'simultaneous feedback'.[5] This was done by exposing some of the translations ('F' and 'G') in the form of a small-scale dictionary and distributing other translations from letters 'H' to 'K' in the form of lists.
Constructive criticism was used as a tool to improve the material included in this dictionary and amendments were made to the original translations. As an example, the original translation for the term 'frozen shoulder' was 'spalla ffriżata'. However healthcare professionals have suggested that 'kundizzjoni fejn ma tkunx tista' tmexxi l-ispalla fid-direzzjonijiet kollha' would be a better Maltese equivalent for this particular term. Also, laymen gave the impression that 'spalla ġġamjata' would be more understood. These two new translations were added to the original translation. Another example is the term 'fracture of skull'. The original translation was 'ksur fl-għadam kranjali' but as suggested by laymen, 'ksur fl-għadam tar-ras' is more comprehendible and the latter translation was then added to the original translation.

English medical term	Original Maltese translation	Final version of translation after the validation exercise
fever blister	nuffata tad-deni	nuffata tad-deni; *ponta tad-deni*
full blood count	għadd ġenerali tad-demm	għadd *sħiħ* tad-demm
full term	il-perjodu normali tat-tqala tal-bnedmin	il-perjodu normali tat-tqala fil-bnedmin, *li tkun għalqitilha ż-żmien*
gastric mucous membrane	membrana mukoża tal-istonku	*l-inforra* tal-istonku
genupectoral position (knee-chest position)	pożizzjoni ġenupettorali	pożizzjoni ġenupettorali; *pożizzjoni fejn l-irkoppa tmiss mas-sider*
gross haematuria	ematurja makroskopika	ematurja makroskopika; *demm viżibbli fl-awrina*
herbal medicine	mediċina erboristika	mediċina erboristika; *mediċina tal-ħxejjex*

Table 1: Validation of terms by laymen and healthcare professionals

Through the process of 'simultaneous feedback', it was found that the majority of translated terms selected during validation by laymen were understood, which confirms that, as required by the Medicines Authority[1], colloquial Maltese was used in the translations.
Additionally, positive feedback was obtained from healthcare professionals, who agreed with most of the translations and with the format of the small-scale dictionary.

It is interesting to note that this dictionary of medical and pharmaceutical terms from letters 'A' to 'K' comprises more than 10, 000 terms and a high percentage (7,049) of these terms were newly translated. The availability of these terms should facilitate the translation process of documents pertaining to medicinal products, particularly patient information leaflets.

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Indication: oral contraception. Composition: Active ingredients: Each wallet (28 film-coated tablets) contains in the following order: 2 dark yellow tablets each containing 3 mg estradiol valerate (EV), 5 medium red tablets each containing 2 mg EV and 2 mg dienogest (DNG), 17 light yellow tablets each containing 2 mg EV and 3 mgDNG, 2 dark red tablets each containing 1 mg EV, 2 white tablets do not contain active substancesContraindications: Qlaira® is contraindicated, if one of the following conditions is present. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately. Deep venous thrombosis or pulmonary embolism present or in history; arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischemic attack); cerebrovascular accident present or in history; presence of a severe or multiple risk factor(s) for venous or arterial thrombosis: diabetes mellitus with vascular symptoms, severe hypertension, severe dyslipoproteinemia; hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and anti-phospholipid-antibodies (e.g.cardiolipin-antibodies, lupus anticoagulant). Pancreatitis or a history thereof if associated with severe hypertriglyceridemia. Presence or history of severe hepatic disease as long as liver function values have not returned to normal. Presence or history of liver tumours (benign or malignant). Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts). Undiagnosed vaginal bleeding. History of migraine with focal neurological symptoms. Hypersensitivity to the active substances or to any of the excipients. Side effects: common side effects reported in clinical trials include headache, abdominal pain, acne, breast discomfort, amenorrhea, dysmenorrhea, metrorrhagia, weight increase. For uncommon side effects and details see package insert leaflet. Dosage and regimen: one tablet is to be taken daily at about the same time on a continuous basis, following the order shown on the blister pack. Each sub-sequent pack is started the day after the last tablet of the previous wallet. Interactions with other medicinal products: contraceptive failure and breakthrough bleeding have been described for the concomitant use of hydantoins, barbiturates, primidone, carbamazepine and rifampicin. Such interactions are also suspected for oxcarbazepin, topiramate, felbamate, HIV-medication (e.g. ritonavir), griseofulvin and preparations containing St. John's wort extracts. Contraceptive failure has also been described for concomitant use of antibiotics, such as penicillins and tetracyclines. Warnings: If any of the conditions/risk factors mentioned below is present, the benefits of combined oral contraceptive use should be weighed against the possible risk for each individual women. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether COC use should be discontinued. All the following warnings and precautions are derived from clinical and epidemiological data of ethinyl estradiol containing COCs. Whether these warning and precautions apply to Qlaira® is unknown.: Vascular disorders with or without indication of arterial or venous thrombosis. The risk is increased for individuals with a respective family history, increasing age, smoking, obesity, dyslipoproteinemia, hypertension, diabetes, immobilization, valvular heart disease, atrial fibrillation, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease, migraine, sickle cell disease. Tumors: breast cancer risk is slightly elevated for women taking combined oral contraceptives. Breast cancer is rare in women under 40 years of age, and the excess risk potentially caused by hormone intake gradually disappears during the course of the 10 years after cessation of combined oral contraceptive use. Experiences from clinical studies do not provide evidence of a causal relation between the use of combined oral contraceptives and an increased incidence of breast cancer. An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies. Annual routine checks by a physician are recommended. Special precautions: Contraceptive safety is impaired if one or more tablets have been missed. Qlaira® is not indicated during pregnancy. Further details see package insert leaflet, valid 16-October 2008. Bayer Schering Pharma AG, European Business Unit Women's Healthcare, 13342 Berlin, Germany, www.bayerscheringpharma.de
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EU.WH.12.2008.0046

Grape Expectations

Wine events

by Albert Cilia-Vincenti

The '*Grape Expectations*' title to these series was thought up by The Synapse scientific editor Ian Ellul. He had initially suggested the setting up of educational wine-tasting sessions for *The Synapse* medical, pharmacist and dental readers. My first reaction had been that tutored wine-tasting sessions would not be easy to set up, as they required considerable time and effort input, both expensive to put together.

We therefore started with the *Grape Expectations* descriptive introductory features to wine appreciation to give us time to think how to eventually organise wine-tasting sessions. As you professionals know very well, the theory is a necessary prerequisite to any skill attainment, but without actual practice of the skill, no real proficiency is possible. So also with acquiring wine appreciation and enjoyment experience – it requires actual practice of tasting wines and not just reading about them.

In his initial choice of the *Grape Expectations* title, Ian Ellul was therefore hinting at the expectation of actual wine-tasting sessions at some stage in the future. Well, perhaps the time Ian was hoping for has arrived. We recently discussed the setting up this year of such a wine-tasting events for medical, pharmacist and dental readers of *The Synapse*. The format will be similar to that of '*Il-Qatra*' wine club which is now 10 years old and has over 60 members.

Let me tell you how *Il-Qatra* wine club started and about its format. In 1996, Wands Ltd, the wine retailing branch of Farsons, organised a wine exhibition at the Manuel Theatre's Isouard Hall. *The Sunday Times* published my write-up about some of the wines on offer for tasting – this feature had important consequences. Apart from the fact it got commented on by '*Roamer's Column*', because no critical wine article had apparently appeared before in this newspaper, it also caught the eye of Dr Antoine Schranz, the winemakers at Marsovin, and some others.

When I bumped into Antoine Schranz soon after, he told me he was surprised to learn that I was interested in wine like he was, and immediately expressed his desire to organise a wine tasting club. Philip Tonna, the Bordeaux-trained enologist at Marsovin, invited me to taste not only the 1995 red *Antonin* and 1995 *Cheval Franc* before these new wines were launched on the market, but he also invited me to a number of blind-tastings of their wines together with other producer's wines. These blind-tastings left me with a lasting impression – that there was no more objective way of comparing wines and judging which you preferred.

Each time I subsequently came across Antoine Schranz, he would ask when we're going to get the wine club started. I can unhesitatingly state that it was his enthusiasm and persistence that eventually got *Il-Qatra* off the ground – he also came up with the '*Il-Qatra*' name. Dr Roberto Balbo, a Sicilian veterinary surgeon resident in Malta, and Mr Mario Mizzi, an accountant, both wine aficionados, together with Antoine and myself, constituted the founding committee of *Il-Qatra*, and us four remain in-charge of *Il-Qatra* as we approach its tenth anniversary.

My main contributions to *Il-Qatra* at its onset were two, namely, that the format of the tasting had to be blind, and that the wine-tasting had to be accompanied by dinner, because wine was invented and evolved to compliment a proper meal and not just a few biscuits or some cheese. The committee decided that members would blind-taste four wines with a monthly dinner, and the first session was held at the former *Bologna* restaurant in Valletta. The club subsequently moved to a number of five-star hotel restaurants and eventually chose the *Petillant* restaurant at Radisson St Julians as its base. The blind-tasting format was slightly refined over the years to the present set-up of members anonymously scoring the wines out of a maximum of 20 points, without any pressure to guess correctly the wines. It is therefore primarily an exercise in learning how to judge wine quality by working out what you prefer and why.

We are proposing a similar format for the *Grape Expectations* wine events with dining at Radisson St Julians because of the consistent quality and experienced service of its *Petillant* restaurant. The first session will be held in the 3rd quarter of this year. Details of the event will be communicated in due course through *The Synapse* Magazine and the *The Synapse* Web Portal.

A Maltese Neurosurgeon in London

by Marika Azzopardi

There is nothing positive about a tragedy, or so it may seem. But a tragedy ignited a young boy's desire to emulate his father and become a neurosurgeon. This is the story of Ludvic Zrinzo.

Meeting the 37-year-old surgeon in Malta recently, I feel lucky to have him for a couple of hours, free from his busy schedule working at the National Hospital for Neurology and Neurosurgery in Queen Square, London. Operating in the first hospital in the world to be dedicated to neurosurgery has been especially significant for the career of 'Zrinz', as his colleagues call him, who has been a neurosurgeon for the past decade.

His father, Laurence Zrinzo, established neurosurgery in Malta with the help of his mother, Sylvia, a neuroradiologist; his uncle Antoine Zrinzo is also a neurosurgeon. "My parents went to the UK in 1971 so that dad could follow his specialisation and I was born there. We eventually returned to Malta when I was 10. My dad always encouraged me to become an architect or an engineer – my own love for maths and physics at school made these sensible choices. His father loves neurosurgery but always felt that there was insufficient local political and infrastructural support for the speciality - he was practically running a one-man show at the time."

Ludvic Zrinzo with his family

However, fate had something up her sleeve. When the Egyptair plane was hijacked in Malta back in 1985, Laurence Zrinzo was in hospital for three whole days, working round the clock to mend the cranial damage caused to the three hostages who had been shot in the head. "I remember dad returning home after his marathon stint at the operating table sporting a beard and visibly exhausted, yet elated. Two of three patients survived and he received commendations from neurosurgeons around the globe. For me, this impressive feat of humanity in a time of tragedy was awe-inspiring. As a result of the teamwork that existed between my parents I immediately set my heart on becoming a Neurosurgeon. Suddenly it seemed a very cool thing to do."

Ludvic Zrinzo qualified in 1995 and stayed in Malta for a while but eventually went up to London with his wife, Mireille, who is a lawyer and had started working in the city. He opted to go for neurosurgical training, taking the opportunity to delve into research, something that he would scarcely have been able to do had he stayed in Malta. He could carry out clinical research directly with patients rather than with test animals in laboratories. He was also awarded a Distinction in his Masters degree in Clinical Neuroscience, which subsequently led him to discover functional neurosurgery and deep brain stimulation.

During the process of his research he came across stem cell transplant results that had surfaced in Sweden and which were especially significant on a specific category of patients who surprisingly manifested symptoms of Parkinson's disease. "These were people still in their 20s and 30s. They had experimented with home-engineered heroin that included the poisonous ingredient MPTP which destroys the same brain cells that die in Parkinson's disease. It was observed that direct injection of stem cells into the brain of these patients worked successfully and it seemed a natural consequence to consider the same treatment to patients with Parkinson's disease. Unfortunately, stem cell therapy in Parkinson's disease has not yet lived up to expectations. However, a different approach, deep brain stimulation, has had remarkable results where stem cell treatment has failed."

The experience got him thinking about the way the brain works and on how research could effectively help to improve surgery. A few rogue psychiatrists and the indiscriminate use of frontal lobotomy practised in the 1950s had shed a dark shadow on the use of brain surgery in psychiatric disorders; yet recently, deep brain stimulation was doing wonders thanks to the implantation of electrodes which worked deep within the brain and could be operated through an implanted pacemaker. Ludvic Zrinzo started work on improving a technique developed by Victor Horsley at the turn of the 20th Century. This neuroscientist and pioneer in neurosurgery had fashioned the Horsley-Clarke apparatus, which was developed together with Robert H. Clarke in 1908. It was used for performing the stereotactic neurosurgery, whereby a set of precise numerical coordinates are used to locate each brain structure. "Thanks to this apparatus and recent research developments carried out in clinical studies, it has been shown that a good percentage of patients with Parkinson's disease can benefit enormously from deep brain stimulation carried out with the help of the stereotactic technique. Whilst medication works well for the first years, its effects may diminish considerably in subsequent ones, eroding patients' quality of life."

"... simply by turning a patient's pacemaker on and off, one can immediately see the results".

Ludvic Zrinzo... deep within the brain

A video demonstrates how Mr Zrinzo operates – the patient remains awake throughout the keyhole surgery procedure, which is assisted by MRI guidance. The operating team can actually see how the electrode being implanted immediately stops the tremor and stiffness of the affected limbs.

"The procedure may appear to be extremely expensive costing a total of £30,000 including £12,000 of hardware value (namely, the pacemaker). However, in the long-term the money that is saved in expensive medication and medical care is phenomenal. After just two to three years it proves to lead to net savings in healthcare expenditure. In fact it is provided free through the NHS in the UK. This surgery has a strong evidence-base - simply by turning a patient's pacemaker on and off, one can immediately see the results. The human brain still requires much exploration, most of it being as yet uncharted territory. I have seen the potential of deep brain stimulation and each operation is a unique opportunity to learn a bit more about how the human brain works. We know it can offer relief to patients with chronic neurological conditions including cluster headaches, depression, Tourette syndrome and a wide range of movement disorders, including the symptoms of Parkinson's disease … the brain is a truly magnificent mechanism. We have merely started scraping the surface."

Mr Ludvic Zrinzo was interviewed when he was in Malta to give a talk on 'Surgical Neuromodulation – Helping patients, advancing knowledge' at the 7th Malta Medical Conference held in November 2009.

Atrial fibrillation: a common arrhythmia with possible dire consequences

by Robert G Xuereb

The diagnosis of atrial fibrillation (AF) is clinched on the electrocardiogram with the finding of fine baseline oscillations, absent P waves and irregular ventricular rhythm.1 It is the most common type of arrhythmia requiring medical care, with a prevalence of 1-2%.2 More than half of AF episodes are detected by continuous ambulatory ECG monitoring. Although uncommon in the younger age groups, less than 0.5% in 40-50 year olds, it affects 5-15% of the population by the age of 80 years.

Classification of atrial fibrillation
- First diagnosed AF is AF presenting for the first time.
- Paroxysmal AF is recurrent and self-terminating AF.
- Persistent AF lasts more than 7 days or is terminated by either electrical or pharmacological cardioversion.
- Permanent AF is longstanding AF.

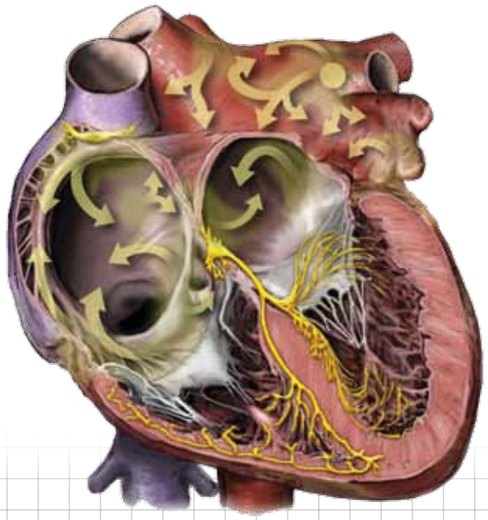
Predisposing factors
Hypertension is found in approximately 2/3 of all patients with AF.3 Uncontrolled blood pressure predisposes to AF. Heart failure is found in 30% of AF patients.3 It can be a consequence of or a cause of AF. Other causes of AF include valvular heart disease especially mitral valve disease, cardiomyopathies, atrial septal defects, coronary artery disease, thyrotoxicosis, obesity, metabolic syndrome, and sleep apnoea. Diabetes mellitus is found in 20% of patients with AF, chronic obstructive pulmonary disease is found in 10% of patients with AF, and chronic renal disease is found in 10-15% of patients with AF.

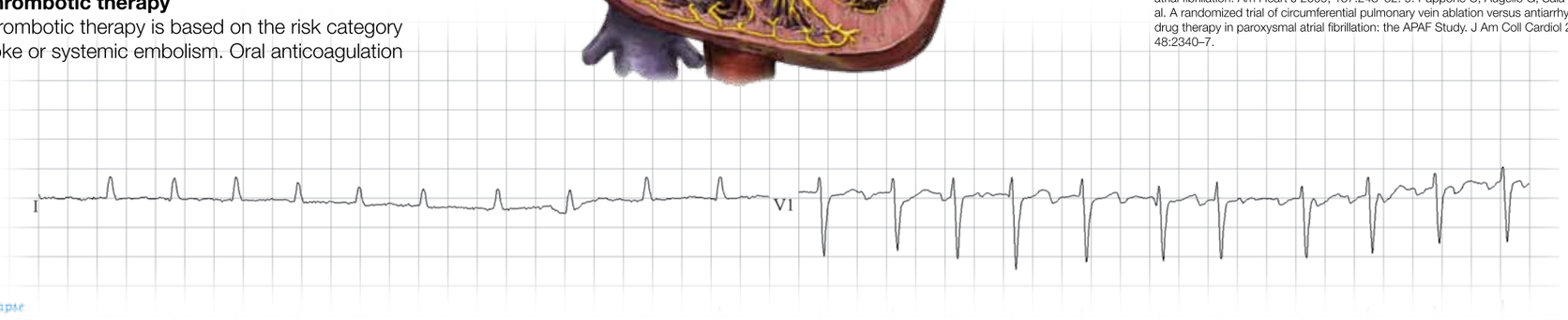
Dire consequences of atrial fibrillation
Death rate is doubled in patients with AF.4 Not only are approximately 20% of strokes due to AF, but these strokes are more severe than strokes of other origins.5 AF also often results in left ventricular dysfunction and in reduced quality of life and exercise capacity.6

Pharmacological therapy for atrial fibrillation
The principles of pharmacological therapy for AF are: (i) antithrombotic therapy, (ii) treatment of underlying condition, (iii) termination of AF, (iv) maintenance of sinus rhythm, and (v) control of ventricular rate during AF.

Antithrombotic therapy
Antithrombotic therapy is based on the risk category of stroke or systemic embolism. Oral anticoagulation therapy with a vitamin K antagonist aiming for an INR of 2-3 is recommended in those patients with one 'definitive' risk factor – previous stroke, transient ischaemic attack, systemic embolus, the elderly (aged> 75) or valvular disease (mitral stenosis or prosthetic heart valves). It is also recommended in those patients with 2 or more 'combination' risk factors – heart failure, hypertension, diabetes mellitus, female gender, age 65-74 years, and vascular disease. If 1 'combination' risk factor is present, either oral anticoagulation therapy or aspirin may be opted for. If no risk factors are present, aspirin 75-325mg daily is recommended.

Antiarrhythmic therapy
The choice of the antiarrhythmic drug for cardioversion as well as for long-term management of AF depends on the underlying heart disease.[1] Class IC agents propafenone and flecainide and the class III agent sotalol are recommended in patients with moderate structural heart disease and hypertension without left ventricular hypertrophy. Amiodarone is the drug of choice in patients with advanced underlying heart disease such as history of heart failure, myocardial infarction, and left ventricular hypertrophy. The class IA antiarrhythmic agents quinidine and procainamide are less commonly used due to their side-effect profile including hypotension, anticholinergic action, AV node blockade, and torsade.





Dronedarone is a structural analogue of amiodarone which is devoid of iodine atoms. It has a better side-effect profile with less risk of pulmonary fibrosis, ocular adverse effects, and skin photosensitivity. The ATHENA investigators have shown that dronaderone reduces the incidence of hospitalization due to cardiovascular events or death in patients with AF.7

Electrical cardioversion
Direct-current cardioversion of AF, the delivery of an electrical shock synchronized with the intrinsic activity of the heart, was first reported by Lown in 1963.8 It is contraindicated in the presence of digitalis toxicity and hypokalaemia, and adequate anticoagulation prior to cardioversion is mandatory.

Ablation of atrial fibrillation
Achieving and maintaining sinus rhythm by antiarrhythmic therapy depends on their limited efficiency and adverse side-effects. A reproducible and effective treatment option of symptomatic patients with paroxysmal AF is catheter ablation with pulmonary vein isolation. Success rates of 70-90% have been reported.9

Conclusion
AF is a growing health problem which is posing a significant economic burden. With an ageing population, the number of patients with AF is expected to double in the next few decades. Effective and early treatment of hypertension and heart failure may reduce the occurrence of AF by delaying damage to the atria. The future of the treatment of AF is promising with the emergence of new antithrombotic medications, better antiarrhythmic agents, and improved ablation techniques.

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Please view the Abridged Prescribing Information overleaf

NAME OF THE MEDICINAL PRODUCT MULTAQ 400 mg film-coated tablets **COMPOSITION** Each tablet contains 400 mg of dronedarone (as hydrochloride). Excipients: Each tablet also contains 41.65 mg of lactose (as monohydrate). **PHARMACEUTICAL FORM** Film-coated tablet (tablet). **Therapeutic indications** MULTAQ is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate **Posology and method of administration** Treatment with MULTAQ can be initiated in an outpatient setting. The recommended dose is 400 mg twice daily in adults. It should be taken as one tablet with the morning meal and one tablet with the evening meal. Grapefruit juice should not be taken together with MULTAQ. If a dose is missed, patients should take the next dose at the regular scheduled time and should not double the dose. Treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting MULTAQ. There is no experience in children and adolescents below 18 years of age. Therefore, MULTAQ is not recommended in this population. Efficacy and safety were comparable in both elderly and younger patients. Although plasma exposure in elderly females was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary MULTAQ is contraindicated in patients with severe hepatic impairment because of the absence of data. No dose adjustment is required in patients with mild or moderate hepatic impairment. MULTAQ is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) <30 ml/min) (see section 4.3). No dose adjustment is required in other patients with renal impairment. **Contraindications** Hypersensitivity to the active substance or to any of the excipients; Second- or third-degree Atrio-Ventricular block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker); Bradycardia <50 beats per minute (bpm); Patients in unstable hemodynamic conditions including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients); Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides, Class I and III antiarrhythmics: QTc Bazett interval ≥500 milliseconds; Severe hepatic impairment; Severe renal impairment (CrCl <30ml/min) **(Please refer to the full SmPC). Special warnings and precautions for use** Patients with stable NYHA class III heart failure or LVEF <35%; Management of plasma creatinine increase; Patients with renal impairment; Electrolytes imbalance; QT prolongation; Patients with galactose intolerance; Interactions **(Please refer to the full SmPC). Interaction with other medicinal products and other forms of interaction** Dronedarone is primarily metabolised by CYP 3A4 (see section 5.2). Therefore, inhibitors and inducers of CYP 3A4 have the potential to interact on dronedarone. Dronedarone is a moderate inhibitor of CYP 3A4, a mild inhibitor of CYP 2D6 and a potent inhibitor of P-glycoproteins (P-gp). Dronedarone therefore, has the potential to interact on medicinal products substrates of Pglycoproteins, CYP 3A4 or CYP 2D6. Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6. A potential pharmacodynamic interaction can also be expected with beta-blockers, calcium antagonists and digitalis. Medicinal products inducing torsades de pointes; Potent CYP 3A4 inhibitor; Moderate/weak CYP 3A4 inhibitors: calcium antagonists; Other moderate inhibitors of the CYP3A4 such as erythromycin are also likely to increase dronedarone exposure such as CYP 3A4 inducer; Effect of MULTAQ on other medicinal products: Statins, Calcium antagonists, Sirolimus, tacrolimus, Oral contraceptives, Beta blockers, Antidepressants, Digoxin, Interaction on warfarin and losartan (CYP 2C9 substrates), Interaction on theophylline (CYP 1A2 substrates). Other products include Pantoprazole (40 mg once daily), grapefruit juice beverages **(Please refer to the full SmPC). Pregnancy and lactation** Pregnancy: There are no adequate data from the use of dronedarone in pregnant women. Breast-feeding: It is not known whether dronedarone is excreted in human breast milk. Fertility: Dronedarone was not shown to alter fertility in animal studies **(Please refer to the full SmPC). Effects on ability to drive and use machines** No studies on the effects on the ability to drive and use machines have been performed. **Undesirable effects** Like all medicines, MULTAQ can cause side effects, although not everybody gets them. The following side effects have been reported with this medicine: changes in the results of one blood test: your blood creatinine level, changes in your ECG (electrocardiogram); problems with your digestion such as diarrhoea, nausea, vomiting and stomach pain; feeling tired; slow heart beat; skin problems such as rash or itching; other skin problems such as redness of the skin or eczema (redness, itching, burning or blistering); your skin being more sensitive to the sun; change in how things taste; losing your sense of taste **(Please refer to the full SmPC). Overdose** It is not known whether dronedarone and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).There is no specific antidote available. In the event of overdose, treatment should be supportive and directed toward alleviating. **MARKETING AUTHORISATION HOLDER:** sanofi-aventis, 174, avenue de France, F-75013 Paris, France. **MARKETING AUTHORISATION NUMBER:** EU/1/09/591/001. For further information please contact Sanofi-Aventis Malta Ltd Tel: 21493022/3

MT-DRO-10-04-01

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Continues from page 13

Referral for further investigation is needed when therapy fails and when there is evidence of organic disease. Abdominal imaging is indicated only when there is doubt about the underlying diagnosis or to reinforce the severity of the problem, should the parents be hesitant to embark on long-term therapy.

There is insufficient data about the long term prognosis of childhood constipation and its persistence into adulthood. A study in the Netherlands found that 60% of children referred to a tertiary centre for chronic constipation where treated successfully at 1 year of follow up. But it also noted that 30% of children followed up after puberty had persistent distressing symptoms.[3] Another study showed significantly better results in children referred to a tertiary centre, with the duration of symptoms less than 3 months before referral.[4]

Constipation and encopresis are potentially curable. Children who follow the appropriate, usually long-term treatment including behaviour modification will eventually regain control of their bowel habits. Long term sequelae include relapse but this can be addressed with repeat therapy, although reassessment for possible underlying organic disease then becomes more pertinent.

Age	Bowel movements per day
0-3 months	2.9 (breast-fed)
	2.0 (formula-fed)
6-12 months	1.8
1-3 years	1.4
More than 3 years	1.0

Table 1:
Normal frequency of bowel movements. *Adapted from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition constipation guidelines, 2006.*

Anatomic malformations i. Anterior displaced anus ii. Pelvic mass (sacral teratoma) iii. Imperforate anus iv. Anal stenosis	**Intestinal nerve or muscle disorders** • Hirschsprung Disease • Intestinal neuronal dysplasia • Visceral myopathy • Visceral neuropathy
Metabolic and gastrointestinal • Celiac Disease • Cystic fibrosis • Hypothyroidism • Hypercalcemia • Hypokalemia • Diabetes mellitus • MEN type 2B	**Abnormal Abdominal musculature** • Down syndrome • Prune belly • Gastroschisis
Neuropathic conditions • Tethered cord • Static encephalopathy • Spinal cord abnormalities • Spinal cord trauma • Neurofibromatosis	**Other** • Cow's milk protein intolerance • Heavy metal ingestion (lead) • Vitamin D intoxication • Botulism

Table 2:
Organic Aetiologies of Constipation in Infancy and Childhood.

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Week 12 — 3 remitters out of 4[3]

Week 24 — 8 relapse-free out of 10[4]

Presentation and Composition: Each film-coated tablet contains 25 mg of agomelatine. **Indication:** Treatment of major depressive episodes in adults. **Properties:** Antidepressant. Melatonergic agonist (MT_1 and MT_2 receptors) and $5HT_{2C}$ antagonist. No influence on extracellular levels of serotonin. Proven antidepressant efficacy including in severe depression. Sustained antidepressant efficacy preventing relapse. Improvement of onset and quality of sleep, without daytime clumsiness from the first week of treatment. No discontinuation symptoms, or effects on sexual function, body weight, heart rate, or blood pressure. **Contraindications:** Hypersensitivity to the active substance or any excipient, hepatic impairment, concomitant use with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin). **Dosage:** The recommended dose is 25 mg once daily taken orally at bedtime. After 2 weeks, the dose may be increased to two 25 mg tablets. **Interactions:** Combination of Valdoxan and alcohol is not advisable. **Side effects:** Common: headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhea, constipation, upper abdominal pain, hyperhidrosis, back pain, fatigue, anxiety, increases serum transaminases. **Precautions:** Not recommended in patients under 18 years old, pregnant woman and during breast-feeding. Not for use in elderly patients with dementia. Use with caution in patients with a history of mania or hypomania and discontinue therapy if manic symptoms appear. Possible effects on the ability to drive a car or operate machinery. Perform liver function tests when initiating treatment, periodically after around 6, 12, and 24 weeks, and thereafter when clinically indicated. Perform liver function tests in patients with symptoms suggesting hepatic dysfunction. Do not use in patients with galactose intolerance or glucose-galactose malabsorption. *As prescribing information may vary from country to country, please refer to the complete data sheet supplied in your country.* **LES LABORATOIRES SERVIER France.** Correspondent: **SERVIER INTERNATIONAL**: 35 rue de Verdun, 92284 Suresnes Cedex – France. **www.servier.com www.valdoxan.com**

1. Lemoine et al. Efficacy of Valdoxan on symptoms relief at week 1 in a comparative study versus ventlafaxine (n=332). *J Clin Psychiatry.* 2007. 2. Lemoine et al. Efficacy of Valdoxan on rsponse at week 6 in a comparative study versus ventlafaxine (n=328). *J Clin Psychiatry.* 2007. 3. Kennedy et al. Efficacy of Valdoxan on remission at week 12 in a comparative study versus ventlafaxine (n=276). *J Clin Psychopharmacol.* 2008. 4. Goodwin et al. Efficacy of Valdoxan on relpase prevention at week 24 in a placebo-controlled study versus ventlafaxine (n=339). *Eur Neuropsychopharmacol.* 2007.

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1 tablet at bedtime

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