Livelife Rehabilitation Centre
pH Impedance testing in gastro-oesophageal reflux
Epigenetic-based treatment for Friedreich’s ataxia
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Budget 2014: Bed of Roses?

If one examines the budget document presented earlier on this month, one can observe various interesting proposals aimed to invigorate our healthcare system. The following is a summary:

- A patients’ charter will be introduced
- The Government will be issuing a White Paper on medicine management and the implementation of the Pharmacy Of Your Choice (POYC) scheme
- “This year, Government will be allocating funding for the purchase of new medicines that are not available at present for dealing with conditions such as Multiple Sclerosis, ADHD amongst children and widening the choice available of medicines including the treatment of diabetes” – Currently paediatric patients are already being given free methylphenidate for ADHD thru’ Schedule V since ADHD is currently classified under ‘Chronic Psychiatric Disorders starting in Childhood’ (as per Act No. I of 2012, amending the Social Security Act)
- 68 new beds will be added to the 925 beds currently found at Mater Dei hospital by 2015
- New services from Mater Dei hospital will be launched. An example is IVF, which will be partly subsidized by the government
- Specialised clinics will be opened, example, eating disorders clinic and lifestyle clinic
- A chemotherapy service is going to be introduced in Gozo - finally
- New services will be launched in Gozo, example, a day care ward and a pain clinic. The Government will also be opening of an eight-bed orthopaedic ward
- New equipment to freeze blood will be purchased
- The administration of health clinics is going to be devolved to local councils
- The opening times of health centres are going to be extended
- The expenses of the second parent who accompanies minors for an operation abroad will start to be paid by the government as well
- Income assessment of claims from separated persons for non-contributory medical assistance will not include the share of maintenance given to spouse

If these initiatives are implemented in an accountable and timely manner, one cannot but commend them.

Interestingly, the POYC scheme is going to be reformed. This has been heralded by the continuous out of stock scenarios which have plagued the scheme since inception. To compound matters, in 2012, the NAO performance audit of the scheme had concluded that there has been a 313% increase in costs incurred over the former health centre-based system. Notwithstanding this, the government has taken the audacious step to announce that it will offer a wider choice of medicines for specific medical conditions, as well as including multiple sclerosis in Schedule V (Yellow card). We will have to wait and see how this evolves.

The government has also reiterated its commitment to work with the private sector. This can be quite challenging since only last April a collaboration on the provision of free emergency service with a private chain of hospitals has been axed. Nonetheless, this public-private partnership will now include the movement of patients from social beds to residential homes in order to maximize the utilization of capacities in both the private and public sectors. This is aimed at reducing the overcrowding currently present in Mater Dei hospital. In addition to this there is going to be a projected 7% increase in new beds by 2015. However one has to wait and see whether these actions will effectively improve the bed management, since apart from an ever-growing elderly population, the prevalence proportion of non-communicable diseases is also set to increase in the future.

In my opinion, tackling the above scenarios will prove to be quite a thorny affair. Let us not forget that the government also intends to publish the report spearheaded by Mr John Dalli on the Mater Dei hospital practices, which will include revelations which as stated by the Hon Prof Edward Scicluna “should shock the tax payer”.

So I guess that John Francis Bongiovi (alias Jon Bon Jovi) would excuse me for using the name of his song for this editorial...

Ian C Ellul
ACLASTA® (Zoledronic acid) 5 mg Solution for Infusion

PRESENTATION: 100 ml solution bottle containing: 5 mg zoledronic acid (anhydrous), corresponding to 5.326 mg zoledronic acid monohydrate. INDICATIONS: Treatment of osteoporosis in post-menopausal women and men at increased risk of fractures, including those with recent low-trauma hip fracture. Treatment of osteoporosis associated with chronic glucocorticoid, cold therapy in post-menopausal women and men at increased risk of fracture. Treatment of Paget’s disease of the bone. DOSAGE AND ADMINISTRATION: Osteoporosis: A single intravenous infusion of 5 mg Aclasta administered once a year. The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks and benefits of Aclasta on an individual patient basis, particularly after 6 or more years of use. In patients with recent low-trauma hip fracture, it is recommended to give the Aclasta infusion two or more weeks after hip fracture repair. Paget’s Disease: A single intravenous infusion of 5 mg Aclasta. Specific re-treatment data are not available for Paget’s disease. Aclasta is administered via a venous infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes. Adequate calcium and vitamin D are recommended in association with Aclasta administration. In patients with recent low-trauma hip fracture a loading dose of 80,000 to 120,000 IU of Vitamin D is recommended prior to the first Aclasta infusion. No dose adjustment in patients with creatinine clearance <35 ml/min, or in patients with hepatic impairment, or in elderly patients. The safety and efficacy of Aclasta in children and adolescents below 18 years of age has not been established. Re-treatment of Paget’s disease: After initial treatment with Aclasta in Paget’s disease, an extended relapse period is observed in responding patients. Re-treatment consists of an additional intravenous infusion of 5 mg Aclasta after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget’s disease are available. Aclasta is essentially anemia-free. CONTRAINDICATIONS: • Hypercalcemia to zoledronic acid or to any of the excipients or to any bisphosphonate. • Hypocalcemia • Pregnancy • lactation. WARNINGS/Precautions: • Serum creatinine should be measured before each Aclasta dose. Aclasta should not be used in patients with creatinine clearance <35 ml/min. • Transient increase in serum creatinine may be greater in patients with underlying impaired renal function. Monitoring of serum creatinine should be considered in at-risk patients. • Patients should be appropriately hydrated prior to administration of Aclasta, especially important for the elderly and for patients receiving diuretic therapy. Use with caution in conjunction with medicinal products that can impact renal function. A single dose of Aclasta should not exceed 5 mg and the duration of infusion should be at least 15 minutes. • Pre-existing hypocalcemia and other disturbances of mineral metabolism should be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly recommended that patients with Paget’s disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget’s disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. • Flare in patients with bone metastases and for patients with Paget’s disease. • Aminoglycosides and diuretics can cause dehydration. • In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase. ADVERSE REACTIONS: • The incidence of adverse reactions (e.g. fever, myalgia, flu-like symptoms, arthralgia and headache) are greater with the first infusion and decrease markedly with subsequent infusions. The majority of these reactions occur within the first three days and were mild to moderate and resolved within three days of the event onset. The incidence of these adverse reactions can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration. Many common: Fever. Common: Flu-like symptoms, chills, fatigue, pain, myalgia, malaise, arthralgia, myalgia, bone pain, back pain, pain in extremity, vomiting, nausea, headache, dizziness, atrial fibrillation, hypercalcemia, nausea, diarrhoea, increased C-reactive protein, infusion site reactions. Uncommon: Hypertension, flushing, palpitations and others. Rare: Abnormalities of blood lipids, abnormalities of liver function test, rash, abdominal pain, gynaecomastia, nausea, vomiting, diarrhea, hypercalcemia, hyperglycaemia, diabetes mellitus, pancreatitis, hypophosphataemia, anaemia. Adverse reactions have been reported including rare cases of a generalized reaction. Common in Paget’s disease only. Please refer to SmPC for a full list of adverse events. LEGAL CATEGORY: POM. PACK SIZE: Aclasta is supplied in packs containing one 100ml bottle. MARKETING AUTHORITY: Novartis Euphorum Limited, Wimbishroom Road, Horsmonden, West Sussex RH12 5AB, United Kingdom. MARKETING AUTHORITY NUMBER: EU/1/95/039/001. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 6, Marsa, MR 1000, Malta. Tel: +356 21222872 2013-MT-ACLASTA-5-SEP-2013
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Livelife Rehabilitation Centre

LiveLife introduces a new concept in private medical care on the Maltese Islands. As the first private physical rehabilitation centre we aim to set the highest standards in rehabilitation through state of the art equipment and quality care given by a multidisciplinary team that offers unparalleled rehabilitation practices.

Our comprehensive care
Professionalism, drive, empathy and state of the art rehabilitative equipment are the tools LiveLife seamlessly combines when working hand in hand with its clients to achieve their rehabilitation goals.

We provide comprehensive care and tailor-made therapy packages whilst placing significant importance on each individual’s well-being. Our aim is to achieve the greatest recovery potential within the shortest time frame, enabling each client to reach their maximum level of functional independence and achieving the quality of life they desire. It is our commitment to exceed our clients’ expectations in every way possible.

Our Services
Individualised treatments are carried out by a team of specialised therapists on both an in-patient and out-patient basis. Our multidisciplinary team is made up of nurses, carers, physiotherapists, occupational therapists and speech language pathologists who are supported by dedicated clinicians and supplementary specialists within the rehabilitation field.

The centre houses a Wellness Centre offering the services of two rehabilitation gyms, an indoor pool, a physiotherapy clinic and outpatient clinics. A multidisciplinary team carries out ward rounds twice weekly during which aims and goals for our in-patients are set up by the team members. This is in conformity with international guidelines to maximise the potential of each individual for rehabilitation and subsequent discharge back to the community.

The rehabilitation gym which can cater for both orthopaedic and neurological conditions is equipped with the latest equipment, including:

• Anti-Gravity Treadmill (ideal for partial weight bearing and weight loss training);
• Standing Tilt Table / Standing frame;
• Suspension gait re-educator for Neurological conditions;
• Electrotherapy units;
• Cardio-vascular training machines;
• Gym resistance stations (for muscle strength training).

LiveLife can offer rehabilitation services for patients with chronic debilitating disease. These include:

1. Acute admissions following respiratory and cardiac conditions;
2. Deterioration in physical well-being such as in Parkinson’s disease or Multiple Sclerosis;
3. General deconditioning in the hospitalised elderly, especially those who are more prone to falls;
4. Post-oncology or palliative care;
5. Post-operative care being either orthopaedic or general surgery.

Rehabilitation will help decrease the length of stay in the acute setting by identifying patients that will benefit from a physical rehabilitation programme with the intention of returning them to their previous level of activity and independence.

Our rehabilitation outcomes help patients settle back into the community, offer support with a continuum of the services provided at LiveLife on a domiciliary basis and create a safer environment that contributes to the improvement of their quality of life. This is achieved by:

• Carrying out personalised home visits;
• Giving recommendations on the lifestyle modifications which are needed;
• Supplying aids needed for functional independence;
• Engaging patients into an out-patient rehabilitation programme closely coordinated by a multi-disciplinary team;
• Regular follow-up visits for all patients to maintain and possibly further improve their rehabilitation achievements.

LiveLife also offers hotel services where as an alternative to hospitalisation, the patient and their relatives can make use of our private rooms and at the same time benefit from our support and rehabilitation services. This way the patient is slowly weaned off intensive caring needs and relies more on his capabilities.

MISSION STATEMENT
As leaders in private healthcare, we are committed to provide a comprehensive and personalised physical rehabilitation programme in a safe, modern environment where advanced medical techniques, effective case management and planning are combined with the strong tradition of our caring. At LiveLife, we strive to empower our clients towards maximising their potential for an improved quality of life.

LiveLife Physical Rehabilitation Centre 46, Manwel Dimech Street, Sliema Tel: 2133 9000

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1. Novartis Europe B.V. Summary of Product Characteristics
2. Novartis Europe Ltd. EUCREAS Summary of Product Characteristics
**Introduction**

Gastro-Oesophageal Reflux Diseases (GORD) are one of the most common reasons for physician consultation. Out of 2,056 individuals randomly surveyed in the United States and Canada, up to 35% had more than one upper gastrointestinal symptom occurring at least once per week with at least moderate intensity.

Investigation of GORD has evolved over the years. It started with the use of barium meals and swallows. These could directly observe the regurgitation of stomach contents back into the oesophagus but were not very good at assessing the damage caused by this reflux. The widespread use of endoscopy enabled direct visualisation of the oesophagitis and any ulceration. However, it was only in the mid 70’s that it was realised that many patients with symptoms of GORD did not have any oesophagitis. Thus the concept of non-erosive reflux disease (NERD) arose.

NERD symptoms are related to the exposure of the lower oesophagus to either acid refluxate or else to non-acid refluxate from the duodenal and intestinal secretions. Management of acid and non-acid reflux is very different and diagnosis and differentiation of the two conditions can only be made by pH and impedance testing.

**pH-Impedance Testing**

This is performed by using a 2.1 mm diameter catheter upon which there are multiple pH and impedance sensors. The catheter is inserted through the nose and is attached to a recorder. The recorder also has buttons which the patient can use to record events such as symptoms, drug ingestion, eating and lying in the supine position.

An impedance sensor basically measures resistance between two probes placed close to each other. Thus it can detect the presence of fluid which will decrease resistance between the probes. Multiple impedance sensors placed along the length of the catheter will not only determine the presence of fluid within the oesophagus but will also show whether this fluid is moving up from the stomach or whether it has been swallowed. The pH sensors determine if the refluxate is acidic or non-acidic.

A pH-impedance recording allows reflux episodes to be classified into liquid only, gas only or mixed. It can determine the height of the reflux and quantifies the number of gastro-oesophageal reflux episodes. It demonstrates the oesophageal acid exposure time and facilitates analysis of the relationship between symptoms and all types of reflux events, both acidic and non-acidic.

Whilst acid reflux often responds to a proton pump inhibitor, non-acid reflux does not and may require surgery.
Friedreich’s ataxia (FRDA) is an autosomal recessive neurodegenerative disorder. It is the most common inherited ataxia in Europe. The neurodegeneration is progressive and normally, within 15-20 years, the patient becomes wheel-chair bound, and ultimately, is totally incapacitated. Affected individuals normally succumb from heart complications. Frataxin (FXN) is a mitochondrial protein that is deficient in FRDA. The deficiency is caused by a mutation within the first intron of the FXN gene which codes for frataxin. Epigenetic mechanisms are responsible in FRDA and epigenetic-based treatment is a potential new strategy to treat FRDA.

Friedreich’s Ataxia is a Neurodegenerative Disease
Friedreich’s ataxia (FRDA) is an autosomal recessive neurodegenerative disorder. The progressive neurodegeneration, mostly affecting spinocerebellar regions, is due to a deficiency of the protein frataxin. Affected individuals suffer from gait disturbances, loss of hand coordination, dysarthria, loss of sensation and loss of muscle power. Diabetes and hypertrophic cardiomyopathy also occur.

Generally, onset occurs before the age of 25 years, but in atypical cases, onset may be delayed or even occur in childhood. Normally, within 15-20 years, the patient becomes wheel-chair bound, and ultimately, is totally incapacitated. Affected individuals normally succumb from heart complications.

FRDA is the most common inherited ataxia in Europe and its prevalence is ~ 1 in 30,000. Frataxin (FXN) is a mitochondrial protein which is deficient in FRDA. Controversy still surrounds its function. However, frataxin is believed to be involved in iron homeostasis inside the cell, acting as an iron chaperone and promoting the biogenesis of haem and iron-sulfur clusters (ISCs) inside the mitochondria. ISCs act as prosthetic groups for several enzymes and molecules, including some that are used inside the mitochondria itself. Thus, frataxin deficiency results in cellular deficiency of these iron-containing enzymes and proteins, mitochondrial dysfunction (decreased Mitochondrial Respiratory Complex I, II and III function) and oxidative damage, destining the cell to death.

The Genetic Mutation in FRDA
FRDA is caused by a GAA repeat hyper-expansion mutation within the first intron of the FXN gene that codes for frataxin. The cytogenetic location of the frataxin gene is 9q13-q21.1. The
The difference between normal and affected individuals lies in the number of the GAA repeat sequences; normal alleles contain less than 30 triplets whereas affected alleles have from ~60 to more than 1000 GAA triplets (Figure 1).

**The Epigenetic Mechanisms Responsible in FRDA**

Mounting research is showing that the molecular mechanism could be an epigenetic silencing of the mutated FXN gene. The chromatin in which the gene lies undergoes epigenetic heterochromatisation, i.e. epigenetic mechanisms cause the chromatin to assume a condensed structure and hence it cannot be transcribed because the transcription machinery is prohibited access to the DNA sequence. Characteristically, the heterochromatisation is brought about by classic epigenetic mechanisms, notably DNA methylation and nucleosomal histone modifications. But other epigenetic molecular players may also have a role, e.g. heterochromatin-protein 1 (HP-1), CTCF (CCCTC-binding factor) and FAST-1 (FXN Antisense Transcript-1). The epigenetic aberrations (also called epimutations) that are commonly found in FRDA are hypomethylation of the nucleosomal core histones H3 and H4 and tri-methylation of the amino acid Lysine in position 9 of histone H3 (H3 Lys9m3). These epimutations involving histones, together with DNA hypermethylation, are very typical of heterochromatin-mediated gene silencing that have also been found in other medical conditions, like cancer (here mostly localised to promoters of tumour suppressor genes).

**Epigenetic-Based Treatment as a Potential Strategy to Treat FRDA**

Definitely, the FXN gene is an excellent target for epigenetic modulation therapy for three valid reasons. First, the most common type of mutation (affecting both alleles) is present in 98% of individuals affected by FRDA. Thus, targeting the epimutated FXN gene is very rational. Secondly, the mutation affects the first intron of the FXN gene. Thus, if the epigenetic aberrations are lifted through epigenetic modulation intervention, it would leave the FXN coding DNA sequence unaffected; transcription followed by splicing would occur and a functioning frataxin protein would be synthesised. Lastly, the heterozygous carriers show no obvious symptoms even though they have ~50% deficiency of frataxin. This implies that a good epigenetic-based treatment only needs to increase the frataxin level to modestly approximate that found in carriers.

To address the epigenetic modulation targeting of the FXN gene, several *in vitro* and *in vivo* models have been devised. These models, besides serving to study the molecular epigenetic hallmarks associated with the mutated FXN gene (see above), are also being used in the search of new epigenetic-based treatments for the disease. For example, Soragni et al. created a molecular model of FRDA that could be used to carry out high-throughput analyses of potential substances. They also showed that the GAA*TTC*-induced transcriptional silencing in their model could be somewhat alleviated by compounds that have already been shown to stimulate FXN expression in human cell lines.

Herman et al. managed to synthesise a class of histone deacetylase inhibitors (HDACis) that reversed FXN silencing in lymphoblastoid cells and in primary non-replicating lymphocytes from individuals with FRDA. These HDACis increased the level of frataxin to those of carriers, and no toxicity was observed. The HDACis directly affected the histones associated with FXN and increased acetylation at particular lysine residues. This class of HDACis were analogous to the compound BML-210. Amongst them, the highly active compound was 4b. A follow-up paper by Rai et al., with almost the same researchers as in the paper by Herman et al., made a further step to assess these compounds as potential drugs...
to treat FRDA. They investigated their efficacy and acute toxicity in an FRDA mouse model (KIKI mouse). One compound was very promising. This was compound 106, a derivative of 4b. This investigation is just an early attempt of epigenetic-based treatment for FRDA. It looks promising but the effect of increased histone acetylation was only evident in the brain for 24 hours after the last injection and had completely disappeared after a week. The KIKI mice just received three subcutaneous doses of compound 106, i.e. once a day for three consecutive days. From this investigation it is clear that further research is needed to see what the correct doses are, in order to maintain the histone modulation continually, without collateral effects (like toxicity) with long term treatments.

Even though, Soragni et al.\(^6\) proposed that their cell line could be adopted for high-throughput analyses in the search for new therapeutics for FRDA, they knew that an appropriate cellular model should not differ greatly from the cell types primarily affected in FRDA, i.e. neurons and heart cells. It was not long that Ku and Soragni et al.\(^6\) found the answer in FRDA iPS (induced pluripotent stem) cells. They reprogrammed fibroblasts into induced pluripotent stem cells which were then differentiated into neurons. They then demonstrated that the FRDA neuronal cells responded to HDACIs. In 2011, permission was given to Repligen Corporation of Waltham, US, for pre-clinical investigation of candidate (RG2833), and Phase I safety trials in human subjects are on their way.\(^9\) HDACIs are surely showing superiority. But epigenetic modulation can also be made through other molecular players. Indeed, translational therapeutic research should also be done with histone methylation reducing drugs (e.g. splitomicin), DNA methylation inhibitors (e.g. zebularine) and GAA-interacting compounds (e.g. pentamidine and DB221).

**Conclusion**

Epigenetic-based treatment strategies are rational and the first generation of epigenetic-based drugs has already been approved by FDA, e.g. for myelodysplastic syndrome. Indeed, the use of such drugs is confirming that epigenetic modulation can be a feasible treatment option, not only for cancer, but also for a growing list of diseases where epigenetic mechanisms of gene expression underline their pathogenesis.\(^11\) Since epigenetic changes are potentially reversible and are thought to be responsible for a wide range of diseases, the scope of epigenetic therapy is likely to expand.\(^15\) And FRDA is surely next in line.\(^5\)

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**References**

5. Pandolfi M. Frataxin deficiency and mitochondrial dysfunction, Mitochondrion 2002; 2:87-93.\(^2\)

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Tricef powder for oral suspension
Tricef 400
1 tablet daily (8 tablets)
Tricef powder for oral suspension
5 mg/kg/day
(40 ml)

Tricef 400 mg, film coated tablets, 60 mL-bottle, powder for oral suspension.

Qualitative and quantitative composition:
Tricef 400 mg, film coated tablets - Cefixime, 400 mg/ tablet; Tricef 20 mg/ml, powder for oral suspension - Cefixime 20 mg/ml.

Therapeutic indications:
Tricef is indicated for the treatment of the following infections when caused by susceptible agents: acute otitis media; acute streptococcal pharyngitis, acute streptococcal tonsillitis, acute lower respiratory tract infections (acute cystitis, uncomplicated acute pyelonephritis); urethritis and uncomplicated gonococcal cervicitis.

Poisoning and method of administration:
Absorption of cefixime is not significantly modified by the presence of food, therefore it may be taken with a meal. Tricef 400 mg tablets - The recommended dose is: in children and children under 12 years (or weighing more than 30 kg): 400 mg daily administered as a single dose. For uncomplicated urinary tract infections a daily dose of 300 mg is effective. Elderly, the same dose do in adults, except for cases of severe renal impairment (see more about the further in this document). Tricef 20 mg/ml (oral suspension) - The normal adult dose is 600 mg/8 h every 12 h. Tricef can also be given in the form of a 4-day course. The dosage is generally the following: children under 12 years the normal dose is 60 mg per kg/day. Patients undergoing chronic peritoneal dialysis or hemodialysis, since cefixime is slowly removed from circulation by dialysis.

Contraindications:
Hypersensitivity to cefixime and to beta-lactam antibiotics in general. Tricef contains 2.52 g of sucrose per 5 mL of oral suspension, and are contraindicated in patients with impaired renal function. Doses indicated above may be given in patients with creatinine clearance of 20 mL/min or above. In patients whose creatinine clearance is less than 20 mL/min, it is recommended not to exceed a daily dose of 300 mg. Patients should also be informed that the treatment may be followed by patients undergoing chronic peritoneal dialysis and hemodialysis, since cefixime is slowly removed from circulation by dialysis. Contraindications related to hypersensitivity to cefixime or its excipients should be respected, and also the dose reduction in renal impaired patients should be observed. Caution should be taken when treating neonates and premature infants, as well as patients with renal dysfunction.

Special warnings and precautions for use:
Tricef should be used with caution during pregnancy and lactation, the contraindications related to hypersensitivity to cefixime or its excipients should be respected, and also the dose reduction in renal impaired patients should be observed. Caution should be taken when treating neonates and premature infants, as well as patients with renal dysfunction.

Forms of interaction:
Antacids do not interfere with cefixime absorption. Tubular reabsorption inhibitors such as probenecid may hamper the renal elimination of the drug. The elimination of cefixime by the kidney is reduced in patients undergoing chronic peritoneal dialysis or hemodialysis, since cefixime is slowly removed from circulation by dialysis. Contraindications related to hypersensitivity to cefixime or its excipients should be respected, and also the dose reduction in renal impaired patients should be observed. Caution should be taken when treating neonates and premature infants, as well as patients with renal dysfunction.

Pregnancy and lactation:
Although animal studies do not suggest any type of toxicity during pregnancy, the safety of cefixime during human pregnancy has not been established. Hence, TRICEF should not be used during pregnancy and lactation.

Effects on the ability to drive and use machines:
No effect on the ability to drive and use machines has been observed.

Undesirable effects:
The undesirable effects are listed in order of decreasing frequency: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (<1/1000). These effects are related to the clinical experience obtained in patients treated with cefixime. They are generally mild to moderate in intensity and may be related to bacterial killing. These effects may lead to the colonization by Candida strains. Pregnancy and lactation:

Presentation:
Tricef 400 mg, film coated tablets, box with 8 tablets.

Marketing authorization holder:
Bial-Portela & Cª, S.A. - Portugal.

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Release sustained strength against COPD with 24-hour Onbrez® Breezhaler®

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Significant reduction in the use of and need for rescue medication

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Available in 150µg and 300µg: two dose strengths allowing flexibility when treating patients with COPD

Onbrez® Breezhaler® allows patients to hear, feel and see that they have taken the full dose correctly

Onbrez Breezhaler® (indacaterol) Inhalation Powder, Hard Capsules

**PRESENTATION:** Onbrez Breezhaler 150mcg and 300mcg inhalation powder hard capsules containing indacaterol mesilate, and one Onbrez Breezhaler inhaler. **INDICATIONS:** For maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). **DOSEAGE AND ADMINISTRATION:** Recommended dose is the inhalation of content of one 150mcg capsule once a day, administered at the same time of the day each day, using the Onbrez Breezhaler inhaler. Capsules must not be swallowed. Dose should only be increased on medical advice. The inhalation of the content of one 300mcg capsule once a day has been shown to provide additional benefit with regard to breathlessness, particularly for patients with severe COPD. Maximum dose is 300mcg once daily. If dose adjustment is required in elderly patients, for patients with renal impairment or for patients with severe hepatic impairment. **CONTRAINdications:** Hypersensitivity to the active substance, lactose or to any of the other excipients. **WARNINGs/Precautions:** Asthma: Onbrez Breezhaler is a long acting 

**Beter2-Adrenergic agonist, which is only indicated for COPD and should not be used in asthma. Long-term beta2-adrenergic agonists may increase the risk of serious asthma-related adverse events, including asthma-related deaths, when used for the treatment of asthma.** 

**Panumidiclonium bicarbonategives patients Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted.** 

**Beta2-Adrenergic agonists may produce significant cardiovascular effects.** 

**Hypokalaemia in some patients, which has the potential to produce cardiovascular effects.** 

**In patients with severe COPD, hypokalaemia may be exacerbated by hypokalaemic and concurrent treatment which may increase the susceptibility to cardiac arrhythmias.** 

**Worsening asthma, irritation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients.** 

**During clinical trials, clinically notable changes in blood glucose were generally more frequent than 2% Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with well controlled diabetes mellitus.** 

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**In patients with severe COPD, hypokalaemia may be exacerbated by hypokalaemic and concurrent treatment which may increase the susceptibility to cardiac arrhythmias.** 

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Malta Pharmaceutical Students Association

MPSA has had a few busy months, in fact we have just launched the official peek and give us feedback on www.mpsa.org.mt This is a page where we can share our upcoming events and where you can get to know about us.

Our Freshers stand on Campus also had a vivacious team ready to meet the new pharmacy students through a buddy system and to answer any queries regarding the pharmacy undergraduate course. We also dedicated a few days to Breast Cancer awareness and distributed leaflets and pink ribbons to those visiting the stand. The MPSA Health Campaigns team together with the Malta Osteoporosis Society (MOS) also organised a World Osteoporosis day which was supported by Servier. This health awareness campaign was held on the 19th October where students carried out the one minute test validated by the International Osteoporosis Foundation (IOF). This is not a conclusive test however it identifies specific risk factors. If increased-risk scenarios were identified, they were referred to their family doctor for follow-up. This could include carrying out the Frax® WHO Risk assessment test, the BMD test and any other treatments or referrals as necessary.

I would also like to share with you some upcoming events; this year the MPSA Health Campaigns team, in collaboration with Kamra Spiżjara has carried out the Diabetes Campaign for the second consecutive year between 12-17 November. Patients got their blood glucose checked out against a small donation and the proceedings were donated to Caritas. This is another initiative which could not have been a success without the active participation of the students and the pharmacies hosting this event.

Last but not least our students also participated in the annual Pharmacy Live-in which was held between 8-10 November. This proved to be yet again a jam-packed activity, with academic activities during the day including seminars, workshops and informative sessions. During the night we cannot not mention the parties organised for the students ... the classic way to break the ice and get to know their colleagues better.

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**QUIZ**

According to the Budget document 2014, what new condition will be included in Schedule V? (TIP: if you read the editorial you would know)

Send your answers by 10th December to ian.c.ellul@gmail.com

The 5th correct entry will win a Medical Language Translator book published by MMSA.

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**Winner of the meal for two at the Tarragon Restaurant in St Paul’s Bay**

Dr Susan Aquilina is the lucky winner of a meal for two at the Tarragon Restaurant in St Paul’s Bay. She has participated in a survey of beliefs and attitudes on antibiotic use in Malta, as part of a Masters degree in Public Health Medicine at the UOM.

Dr Aquilina MD FRCP is a Dermatology Consultant at Sir Paul Boffa Hospital in Floriana. She graduated from the University of Malta Medical School in 1997 and has been working at the Department of Dermatology at Sir Paul Boffa Hospital since 2000.

**Winner of the Medical Language Translator book published by MMSA**

Mr Noel Pace BSc(Hons.) Pharm Sci M.Pharm. is the winner of the Medical Language Translator book published by MMSA. He was the 5th participant who replied correctly to the question, “When will the 23rd Alzheimer Europe conference be held?” The correct answer was 10 – 12th October 2013.
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What we didn’t expect

The day when students find out that they are eligible for enrolling into the Doctorate of Medicine and Surgery course is remembered by many as one of the happiest days of their lives. The moment you actually do, you are introduced into a welcoming faculty and a brilliant organisation which makes you feel like you’ve joined a rather large family rather than an undergraduate course.

After the post-results’ glow wears off and the excitement of joining a new course dampens down, most medical students discover a feeling which is eventually nourished. For any medical student, having the privilege of participating in a study program in a foreign country, it is quite evident that in Malta we own a particular sense of pride. This is not the extravagant obnoxious pride which was the fault of some paternalistic predecessors, but a gentler pride, a drive to preserve the faith which the public holds in our profession. Reflected in a powerful student organization and a faculty which strives to empower the medical student with the knowledge to become a good doctor, it is easy to see that in this country we still believe the medical profession to be a trustworthy role. Each medical student feels the need to prepare himself or herself to become a good doctor. The thing about medical school is that you are never prepared of how much it will affect every aspect of your very existence. In the faculty’s defense, lecturers and older students do try to warn you about the student struggles. You receive advice about handling difficult situations whilst being drilled over and over again with conditioning words which are meant to help you become a good doctor ... “Be assertive”, “Be empathic”, “Study smart, not hard”, “Question everything”, “Talk about your feelings” and on and on ... the advice never ceases.

However, here’s the pitfall and the beauty of the medical school - it will definitively surprise you. We have yet to meet a medical student who has experienced what they had initially expected from medical school. No one can prepare you for seeing the first patient die, or from seeing your first birth, for days filled with more studying than is sane for any human being, for the bonds you form with your classmates, the admiration you acquire for your lecturers and most of all the respect you come to earn for yourself.

It is in these small surprises and unplanned moments that you realise that the reason why you drag yourself through the difficult and sometimes seemingly impossible parts of medical school is because in the end, the good times, are worth it.
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Despite effective blood pressure and cholesterol-lowering drugs, atherosclerotic cardiovascular disease remains the major morbidity and mortality causation in developed countries. The disease-causing lesions originate from benign-looking, non-occlusive, lipid-laden plaques in childhood (fatty streaks) on the internal surface of arteries. These progress to enlarged plaques (atheromas) characterised by accumulation of lipids, chronic inflammatory cells, connective tissue and an overlying fibrous plaque. Their progression leads to stenosis or occlusion of small and medium-sized arteries.

Atherosclerotic plaques are also described in terms of complexity and resultant instability. Complexity depends on degree of inflammatory cell infiltration, lipid deposition, calcification and intraplaque haemorrhage. Such complex plaques are unstable and prone to rupture. There is therefore an inflammatory mechanism to plaque instability. Plaque rupture exposes the thrombogenic atheromatous core which leads to sudden thrombotic occlusion of small to medium-sized arteries, such as coronary ones, with familiar serious consequences of unstable angina, myocardial infarction, or sudden death. Stable atherosclerotic lesions are slow-growing, less complex and have dense fibrous caps. They allow a collateral circulation time to develop, are less likely to rupture and are therefore less threatening.

Aortic atherosclerotic plaques are mainly confined to its abdominal portion. The aortic lumen is too wide for ruptured plaques to cause aortic thrombotic occlusion, but they may weaken the arterial wall and cause abdominal aortic aneurysm. Intermittent showers of tiny thrombi from ruptured aortic plaques are likely to end up in renal and leg skin arterioles, eventually leading to renal failure and lower limb ischaemic problems.

Atherosclerosis is now recognised to be fundamentally an inflammatory disease. The inciting event is dysfunction of the arterial inner lining cells (endothelium), leading to inflammatory cell infiltration and release of proinflammatory cytokines within the arterial wall. Low density lipoproteins (LDL) are thought to be more likely to be trapped in the lesion when oxidised. Smooth muscle cells of the arterial wall are triggered to migrate into the plaque and to produce a collagen-rich matrix and a fibrous plaque.

Cardiovascular risk factors promote atherosclerosis by damaging the endothelium – the latter is involved in regulating vascular tone, inflammation and thrombosis. Healthy endothelium releases nitric oxide (NO) to induce vasodilatation in response to, say, platelet aggregation. NO also reduces expression of adhesion molecules to prevent macrophage infiltration and dampens vascular smooth muscle cell proliferation. These are protective mechanisms against atherosclerosis. Cardiovascular risk factors such as smoking, hypertension, diabetes, obesity and hypercholesterolaemia induce endothelial dysfunction through mechanisms such as free radical oxidation, haemodynamic strain and genetic pathways. Dysfunctional endothelial cells (EC) acquire a...
proinflammatory phenotype, expressing chemokine receptors, decreasing NO production, and dysregulating cytoskeletal and junctional proteins2,3.

A non-invasive ultrasound-based test of endothelial-dependent vasomotion, termed “flow-mediated dilatation”, measures brachial artery diameter change and has been used to detect early endothelial dysfunction2. However, it requires highly trained operators, expensive equipment, and minimisation of environmental and physiological influences.

One can biochemically assess EC dysfunction with use of EC markers. Many candidates, such as NO, inflammatory cytokines, adhesion molecules, thrombosis regulators and markers of endothelial repair have been assessed, but have not proven to be clinically viable2. Endothelial microparticles (EMP), which are small vesicles released during cell activation or injury, are elevated in patients with atherosclerosis2. Since EMPs can be quantified, they are promising candidates for clinical testing.

Lipids within atheromatous plaques are susceptible to oxidation by several enzymes. Oxidised LDLs (oxLDL) are cytotoxic to arterial endothelium. Macrophages migrate from bloodstream towards accumulated lipid in plaques, take up LDLs to degrade them, but oxLDL are resistant to degradation. Diets deficient in antioxidant vitamins and minerals may therefore accelerate oxLDL accumulation in plaques and atheromatous progression.

Besides reducing LDL concentrations by blocking cholesterol synthesis, statins also inhibit inflammatory pathways and increase NO production, which enhance endothelial protection4. They also lower cytokine production and inhibit recruitment, migration and cell adhesion to endothelium4.

The role of high density lipoproteins (HDL) on atherosclerosis has received attention. Torcetrapib, a cholesteryl ester transfer protein inhibitor, increases HDL and decreases LDL cholesterol levels but does not significantly reduce coronary atheroma volume5. Another recent approach involves synthesizing fusion proteins of oxLDL binding receptors and the Fc domains of immunoglobulins6. Zeibig et al (2011) created a soluble dimeric fusion protein Fc–CD68 capable of specific high-affinity binding with oxLDL in atherosclerotic plaques, reducing oxLDL uptake. This compound reduced lipid deposition by one third and aortic plaque extension by nearly 50%6.

Some American cardiologists have produced clinical evidence that atherosclerotic progression can be halted, and to some extent reversed, by dietary modification and lifestyle changes (exercise and stress management) alone, and suggested that up to 90% of cardiac surgical interventions may potentially be unnecessary7. Many patients, however, will not modify their diet and change their lifestyle. The quest for more effective and safer anti-atheromatous drugs will therefore remain clinically and commercially important, not least because current statins are associated with side-effects in 10-15% of patients. They inhibit production of coenzyme Q10, which may increase risk of heart failure, and some American cardiologists recommend coQ10 supplements with statins.

Inflammation is a complex immune response to pathogens or other tissue damage. Clinicopathological and experimental studies have shown that a large variety of inflammatory cells and cytokines are involved at all stages of atherosclerosis. There have also been recent claims of an association between poor oral hygiene with risk for atherosclerotic cardiovascular disease, possibly because bacteria (or bacterial proteins), released into the bloodstream from inflamed gums might promote inflammation within atherosclerotic lesions.

Despite our greater understanding of atherosclerosis pathogenesis, many challenges remain in its diagnosis and management. Coronary angiography is still the gold standard for identifying risk lesions, although detection of subtle but significant plaques is problematic. Novel imaging modalities have the potential to provide valuable information about extent of lesions in a relatively non-invasive manner. These include intravascular ultrasonography, thermal imaging, and high-resolution magnetic resonance imaging9,10. Magnetic resonance and nuclear imaging that harness molecular mediators of atherogenic inflammation as targets have generated considerable interest12. However, these modalities are not yet ready for clinical application.

Besides elevated LDL, high glucose15 and triglycerides16 (and low HDL17) are associated with sharply higher atherosclerotic disease risks. Low DHEA (dehydroepiandrosterone-sulfate) blood levels are also associated with higher rates of endothelial dysfunction and heart attack18.

Biomarkers are measurable parameters which can serve in diagnosis, treatment follow-up, and prediction of disease progress. Due to the pivotal role of inflammation in atherosclerosis, C-reactive protein (CRP), measured by a highly sensitive assay (hsCRP), has gained attention11. In a study reported in 2002, women with elevated hsCRP were twice as likely to suffer a heart attack or stroke compared to women with high LDL levels13. Another study demonstrated that individuals with an elevated hsCRP have high vascular risk, even when cholesterol levels are considered within normal range12. However, elevated hsCRP is also a marker of cancer. Many other biomarkers associated with progressive atherosclerosis have been investigated – lipoprotein-associated phospholipase A2 (PLAC Test) is the only one currently approved by the FDA14. However, it will not distinguish between unstable plaque in coronary, carotid or aortic locations. Although none of these biomarkers have become routine in clinical practice, they have the potential of becoming so, because around 50% of heart attacks and most strokes occur in people with cholesterol levels within normal limits.

A region on chromosome 9 has been identified as being associated with cardiovascular diseases and genetics may therefore play a role in predicting atherosclerosis risk12. Considerable investigative effort in years to come is still necessary, and clinicians need improved, preferably non-invasive, tools to identify and manage patients with clinically significant atherosclerosis.

References from thesynapse.net
Our previous reviews have inspected the intersection of literature and medicine. This essay will detail some specific and important medical characters in mainstream literature, expanding on the title of this essay: ‘[w]e have not lost faith, but we have transferred it from God to the medical profession’,¹ as well as a reading of a textbook that specifically details the topic.

This is, perforce, a superficial appraisal as the material has been extensively and broadly reviewed in journals such as Literature and Medicine and Medical Humanities which are devoted to exploring interfaces between literary and medical knowledge. Some excellent books have also focused on this topic, such as Norman Cousin’s The Physician in Literature (1982),² and we will now review this text in some detail.

Norman Cousin’s The Physician in Literature (1982) illustrates the myriad ways in which doctors are portrayed in mainstream classics. This anthology contains short stories, essays, poems and excerpts that highlight doctors and medicine in classical literature. Literary selections are organised into self-explanatory categories which include Research and Serendipity, The Role of the Physician, Gods and Demons, Quacks and Clowns, Clinical Descriptions in Literature, Doctors and Students, The Practice, Women and Healing, Madness, Dying, The Patient, and An Enduring Tradition.

Cousins’ introduction calls forth an interesting argument in that doctors are trained to utilise the scientific method of inductive reasoning, appreciating errors and performing self-corrections. This allows practitioners to remain updated in medical advances. However, the art of the actual practice of medicine remains unchanged. Writers, on the other hand, deal with absolute and immutable human values that defy and transcend change. Cousins, for example, comments on Pasternak’s Dr. Zhivago (1958),³ which demonstrates that a doctor’s skill ‘depends as much on his knowledge of life as it does on his knowledge of disease’.²

Hans Zinsser’s autobiography As I Remember Him (1970) is frequently mentioned throughout.⁴ Zinsser was a microbiologist who made major contributions to bacteriology and public health. He also strove to understand the meaning of life and to act as a liaison between medicine and the general public, in true interdisciplinary fashion.

The pathos of life and disease, both in literature and in authors’ lives, is repeatedly highlighted in this anthology of essays. The successive chapters frequently deal with negative portrayals of doctors and medicine in mainstream literature, and while not stated explicitly, doctors are often viewed in one of two ways: ineffective quacks or rogues, often tinged with arrogance and conceit and a specific example will be cited.

George Bernard Shaw’s The Doctor’s Dilemma (1906) depicts an obvious medical choice that is inextricably woven with, and complicated by an ethical quandary. Moreover, the play places the entire Edwardian medical establishment on stage, and depicts a surgeon who invents a useless operation on a nonexistent organ, the removal of the ‘nuciform sac’. The thesis of the play was revolutionary for its time as it posed the hitherto almost never voiced possibility that doctors may feel that they need to perform unnecessary operations in order to earn their livelihood. The play was aimed to parody Sir William Arbuthnot-Lane, 1st Baronet, who was a Scottish surgeon, and separates doctors into two types, the arrogant and conservative diehards who practice the venerable art of medicine, and the humane, modern scientific practitioners.⁵ Shaw was greatly influenced by two doctor friends, and he criticised some doctors for being poor and ignorant, conceited and often only availing themselves of obsolete and spurious knowledge, lambasting surgeons who commence operating without even an hour of practice. He also condemned doctors who behave like mechanics, treating diseases with no care as to their cause. He argued that doctors should behave like biologists, with fundamental knowledge that permits the treatment of cause and not just effect.

It is also worth noting at this point that this play may also have been poking fun at Dr. Isaac Baker Brown who advocated and performed clitoridectomy (surgical excision of the clitoris) at his London Surgical Home in the 1860s.⁶ The evil physician features not only in mainstream literature, but occasionally also in science fiction, and only one example will be given here, the classic Caduceus Wild (1959) by Moore wherein doctors are not witnessed in their medical capacities but as world oppressors and outright tyrants in the trope of Big Brother.

Medical students are also susceptible to this brand of arrogance, and Arrowsmith (1925), a novel by Sinclair Lewis, is used as a typical example.⁷ Indeed, in a later chapter, Oliver Wendell Holmes’s valedictory address to the graduating class of Bellevue Hospital, The Young Practitioner (1871) is mentioned. This cautions the new doctors that their knowledge will soon be forgotten if unused, and that the
possibility of new acquisitions of knowledge should never be outgrown, among other practical advice.\textsuperscript{9}  
The next section will cite some specific examples of doctors and medicine in literature, including Pangloss, Caius, Hyde, Manette then finally focussing Lydgate.

An example of a semi-medical individual is Pangloss, a character in Voltaire’s novel \textit{Candide} (1759) who is described as an individual with a vast breadth and depth of lore, including medical knowledge. Throughout the play, he has few personality traits and these do not evolve. Pangloss contracts syphilis, becoming weakened and deformed, and is unable to obtain a cure as he has no money. When a benefactor finally materialises, a cure is obtained, albeit with the further loss of an ear and an eye. Pangloss stoically rationalises syphilis, stating that it was necessary for this disease to be brought back by Colombus and his men from America along with other New World wonders such as chocolate.\textsuperscript{10}

Medicine in literature also reflects the practices of the times. For example, William Shakespeare’s era was an exceptionally chaotic period for medicine in England, laced with quacks and empirics who practiced unsafely. Shakespeare himself was influenced by medical practice and was [a]n astute observer and an insatiable reader of the many books in print. Some of these were the works of old masters—Hippocrates’ \textit{Aphorismi and Prognostica}, Galen’s \textit{De usu partium}, and Celsus’ \textit{De Medicina}. Other, more ‘modern’ works included Vesalius’ \textit{De Humani Corporis Fabrica}, Pare’s \textit{Apologie and Treatise}, Vicary’s \textit{A Profitable Treatise of the Anatomie of Mans Body}, Caius’ \textit{Boke or Counsell against the Disease called the Sweate}, Boorde’s \textit{The Breuiary of Helthe}, Bullein’s \textit{Bulwark of Defence against all Sicknes, Sores and Woundes}, and Bright’s \textit{A Treatise of Melancholie}.\textsuperscript{11}  

Furthermore, in the late 1500s, Shakespeare lived close to the infamous psychiatric hospital of St. Mary of Bethlehem (Bedlam). He later moved to Cripplegate, close to the Barber-Surgeons’ Hall, where three annual public demonstrations in anatomy were regular attractions. Moreover, Shakespeare’s eldest daughter married John Hall, a Cambridge graduate in Arts with medical training. Unsurprisingly, virtually all of the common diseases in Shakespeare’s time are mentioned in his plays along with perceived aetiologies that were attributed to various imbalances of the four bodily humours ie sanguine, choleric, melancholic and phlegmatic. Interestingly, the later plays also reflect the then diminishing importance of the classical views of Galen due to the ascendancy of the new masters of medicine, such as Vesalius. Specifically, in this period, the correct treatment of wounds was crucial and life-saving, and the Galenic theory mandated the wound formation of ‘laudable pus’. For this reason, wounds were packed and dressed with greasy, irritating and therefore highly infective unguents, a potentially fatal practice maintained until the Listerian era.

Surgeons are frequently sought in Shakespeare’s plays in order to treat wounds and while the speciality of orthopaedics had not yet been introduced, Shakespeare was fully aware of its importance, with attendant deformities, fractures and dislocations, usually the result of violence: domestic, criminal, civil or war. The importance of syphilis is also stressed, along with its debilitating effects on the central nervous system and on joints and bones.

Shakespeare’s profound grasp of disease and its contemporary treatment was first chronicled by Dr. Charles Bucknill in \textit{The Medical Knowledge of Shakespeare} (1860).\textsuperscript{11} However, it should be noted that in these plays, disease is almost invariably a metaphor, a representation of moral weakness in an individual, professional or in a society. It was thus that well into the 18\textsuperscript{th} century, doctors were frequently (and often correctly) deemed quacks and impostors, beneficiaries of the suffering of others.\textsuperscript{8}

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World Diabetes Day

It is estimated that at least 347 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of fasting high blood sugar. A similar number of deaths have been estimated for 2010. The published data for Malta through the International Diabetes Federation’s Diabetes Atlas estimate that the diabetes prevalence in Malta is 9.8% of the adult population, representing 29,900 people. The atlas forecasts a rise in prevalence to 11.6% of the adult population, representing 36,600 people by 2025.

There is strong evidence from randomised, controlled trials that lifestyle interventions incorporating diet and physical activity can prevent Type 2 diabetes in high risk individuals. The most dominant predictor for Type 2 diabetes prevention is weight loss. It is estimated that for every kilogram lost, it is associated with a 16% reduction in risk. A large trial in the United States has shown that lifestyle interventions including a low-fat diet, significantly reduced body weight, HbA1c and cardiovascular risk factors and these positive changes could be maintained over four years.

Diabetes and the diet

Technical reviews on the evidence for the nutritional management of patients with diabetes indicate that the most important dietary advice to people with diabetes is to choose a healthy well-balanced diet; with meals and snacks carefully planned to minimise changes in blood glucose concentrations. This can be achieved via the consumption of normal day-to-day foods. On the other hand, weight management should be the primary nutritional strategy in managing glucose control in Type 2 diabetes for people who are overweight or obese.

A person with diabetes needs to eat a varied, balanced diet based on the four food groups:
1. bread, cereals, wholemeal pasta, rice and potatoes;
2. fruit and vegetables – two portions of fruit and three portions of vegetables are recommended daily;
3. low fat milk, yoghurt and cheese;
4. low fat meat, fish, legumes, eggs and nuts.

Diabetes and exercise

Being active is very important for everyone and especially for people who have diabetes. Physical activity has clear benefits on cardiovascular risk reduction and glycaemic control in people with Type 2 diabetes, with a meta-analysis reporting a mean weighted reduction of 0.45% to 0.65% in HbA1c. It is also recommended to perform moderate physical activity for at least 30 minutes five times a week. This can include going for brisk walks, using the stairs instead of the lift, and walking instead of using the car.

As a health provider you have a crucial role in encouraging your patient to lead a healthy lifestyle. Patients can consult the booklet ‘Id-dijabete u l-Ikel’ from the Health Promotion and Disease Prevention Directorate for further information.

References
Sunday lunches are always popular with the family and this time of year brings again the table gathering for an afternoon of chat, gossip and story-telling from the summer fun! Here are some ideas on how to come up with your best Sunday lunches at home.

Look into your favourite recipe book some days in advance and get the day planned well. Go through the ingredients list and ensure you got all available by Saturday morning. Prepare any soups, sauces, marinates, stuffings and anything that can save you time on Sunday, like peeling and chopping vegetables.

Get your kitchen ready and prepared by Saturday evening. You might need to look into increasing some worktop space by clearing items not required. The table can also be set on Saturday evening so on Sunday you can focus mainly on the cooking.

On the day start with a good breakfast and get other members of the family to wake up to it so then all can give a helping hand to prepare for lunch. Roasts can be very ideal since a joint of meat can be ordered as required from your butcher. This can come ready seasoned and stuffed according to your liking.

Surprise your guests with some innovative alternatives or dishes with a twist. Some nicely chilled prosecco with a nice selection of small finger sandwiches not only entices the appetite but keeps your guests busy; thus avoiding them from getting into your kitchen while getting all ready.

For starters include an old favourite family dish. A prawn cocktail or a lasagne works miracles and is quick to serve! Think about children’s favourites and ensure to get their meal ready and served before everyone else. If room is available, set their own table in an attractive format with coloured napkins and some funny decorated fruit. Take good care of the food requirements for the elderly and possibly a quiet area for their afternoon nap.

The invitees may ask you if they need to bring something along, and dessert can always be asked from them. It will be everyone’s pleasure to get their speciality dessert and this can provide an array instead of a single type. If not, you can always keep it simple by serving cheeses and biscuits. Liqueurs and coffee at the end are appealing. Avoid instant coffee but brew some fresh. It will take the same time to prepare and brings aroma in the house.

There’s no better lunch than your Sunday lunch at home with the family. It not only guarantees quality home cooking but encourages the family to spend time together and to enjoy quality time ... something which today is become quite a challenge to achieve.

SOME USEFUL TIPS

- Fresh flowers on the dining table make it look better
- Wash and polish glasses that have been stored for long
- Avoid delays by inviting guests 20 minutes earlier
- Consider having snacking options for the late afternoon
- It is impolite to refuse help to clear and clean after the meal
I write this interview against the news backdrop of a substantial measles outbreak in Wales which took the authorities by surprise and has infected 1,219 persons. 88 patients have been hospitalised and one patient died. According to BBC News, the outbreak has elicited the emergency administration of 50,000 non-routine vaccinations across this part of the UK, whilst over 40,000 high-risk youths remain unvaccinated. Fortunately, Public Health Wales declared that the saga officially ended last July. And I think back to what Mark Muscat told me about measles ... “The World Health Organization Regional Office for Europe had planned to eliminate measles in the European Region by 2010. It did not succeed. The new target is now set for 2015.”

During the interview I had looked at him askance, and with medical news such as that which emerged from Wales, it seems unlikely that the elimination goal by 2015 is such a likely accomplishment. But what is the connection between Dr Mark Muscat, measles and WHO?

Mark Muscat graduated as a doctor in Malta in 1989 and proceeded with a Master in Tropical Medicine (Liverpool) which he supplemented with his stints in Kenya and Tanzania, working in the field. Then he followed a Master in Public Health (Malta) and a post within the Department of Public Health as a public health specialist. The next move took him up north, all the way to Copenhagen, Denmark to take up the post of co-ordinator for the then newly established European surveillance network for vaccine-preventable diseases, alias EUVAC.NET.

The job entailed the solidification of surveillance on vaccine-preventable diseases, as well as the implementation of policies linked to such work at a European level. In September 2011, EUVAC.NET was integrated into the activities of the European Centre for Disease Prevention and Control, based in Stockholm, Sweden. That same year he completed his PhD on the challenges of eliminating measles in Europe.

Mark now works in the Vaccine-Preventable Diseases and Immunization programme of the WHO European Regional Office in Copenhagen. He describes measles as one of the most infectious disease known to mankind, it being airborne and highly contagious. “Even whilst the combined measles, mumps and rubella (MMR) vaccine was believed to be the be-all and end-all of measles, the Wakefield article published in The Lancet in the late 1990s (later on discredited) was instrumental towards some serious scaremongering that caused innumerable parents to opt against vaccinating their children. The report was highly publicised in the UK especially, and this led the UK measles vaccination coverage to decline significantly. This is partly the reason why measles is still endemic in the UK. However, outbreaks still flare up in other countries of the European Region, which includes not just the European Union, but also the ex-Soviet Union countries. Whilst the Region of the Americas has been declared officially free of measles, this is not the case in the WHO European Region. During 2008-2011 over 20,000 cases of measles were reported in France. Ten patients died from complications. In 2009-2011, an outbreak in Bulgaria resulted in over 24,000 cases of measles and 24 deaths. Currently, there are ongoing large-scale outbreaks of measles affecting hundreds of persons in Turkey and Georgia. During the first six months of 2013, six measles-related deaths were recorded in the European Region, Mark notes that elimination is not eradication. Elimination aims at stopping the endemic transmission of measles, yet there can still be minor outbreaks caused by the importation of the virus, which outbreaks would however, be small and quickly contained. He explains that this human disease usually presents in a mild form in children with fever, rash, runny nose, watery eyes and cough. However, some infected patients, particularly infants and adults, may develop...
complications such as pneumonia or acute encephalitis. “Invariably fatal is the manifestation of sub-acute sclerosing pan-encephalitis. This can occur years later and manifests itself with an abnormal gait, episodes of epilepsy and a fatally deteriorative state.”

The key strategy to eliminate measles is to vaccinate widely, to cover at least 95% of the population – the minimum percentage required to eliminate the disease. “The success of the vaccination programme depends on reaching such high vaccination coverage and vaccinating those still susceptible to the disease.” The first dose is usually given at 12 months of age with a second dose being administered at a later stage, during childhood, to reach out to that small percentage (5%) of patients who do not respond to the first dose.

“Reaching high levels of vaccination in the population is today presenting new challenges since many people are more afraid of the vaccine rather than the disease itself. One can say that in this instance, we are becoming victims of our own success. It becomes increasingly difficult to see the benefits of vaccinating against disappearing diseases when you don’t appreciate the risks of these diseases.” Compared with other vaccines such as the polio vaccine, the MMR vaccine is not mandatory and is only ‘highly’ recommended. This does not make it less important but, “protecting our society against vaccine-preventable diseases relies heavily on the goodwill of the public as well as the healthcare professionals’ positive recommendations towards vaccination.”

“The success of the programme also relies on a very good surveillance system which in turn depends on the constant collaboration with healthcare professionals.” Doctors and other healthcare professionals are urged to notify any suspicious cases and confirm them with laboratory tests. Yet, Mark admits that there are potentially serious failings on the part of those doctors who have never seen one single measles case during their training or practice. This means that they may not recognise the disease when they encounter it.

“Recognising a disease never witnessed before is a huge challenge.”

Who is getting measles today?
“This was part of my research which highlighted that unvaccinated individuals as susceptible individuals. These include individuals who are not eligible for vaccination such as infants too young to be vaccinated and those few with contraindications to the vaccine. These susceptible persons can only depend on population immunity, so-called herd immunity, to protect them. Then, there are specific vulnerable populations like the Roma ethnic minority groups in many European countries mostly in central Europe, orthodox Protestant communities in the Netherlands and followers of anthroposophic teachings mostly in German-speaking countries.”

In 2013, the World Health Organization Regional Office for Europe has started to verify elimination of measles with individual countries of the Region, and these will have to show 95% vaccination coverage and good performance on other indicators, to be given the all-clear. “As a public health specialist I have plunged myself in my work on the elimination plan, reporting on measles outbreaks, providing technical assistance to countries and advocating for the elimination of measles.”

So, is there another side to Mark?

Indeed there is. This 48-year-old also enjoys travelling, photography, reading, gardening and cycling, using the bike for 15km daily, rain or shine, to work and back. A more recent passion is that of iconography and the writing of icons in the traditional way using egg tempera on wood. “The art of writing icons leads to the contemplation of that which is divine and spiritual.”

I feel fortunate to have grabbed some of his little time during his recent short stay in Malta ... perhaps his next visit will bring positive updates on the measles front.
MR Imaging of early Rheumatoid Arthritis and Spondyloarthropathy – Part II

Bone marrow oedema may be seen alone or surrounding bone erosions (Fig 2-3) and is considered to be a potentially reversible phenomenon. Histologic studies of joint replacement specimens have shown that bone marrow oedema corresponds to inflammatory cellular infiltrates in the bone marrow, representing osteitis. Bone marrow oedema is considered to be a very early marker of inflammation, given that its presence correlates with increased levels of acute phase reactants (erythrocyte sedimentation rate and C-reactive protein) and the clinical stage of disease activity. Bone marrow oedema is also closely related to the degree of synovitis and has been associated with subsequent erosive damage; as a result, it is currently considered to be a ‘forerunner’ of erosions.

The detection of erosions in patients with early rheumatoid arthritis is a key imaging finding, since it indicates irreversible joint damage. On radiographs, the presence of erosions is suggested by the loss of visualization of the bone cortex. MR imaging helps detect more bone erosions in the wrist and hand in early rheumatoid arthritis (Fig 4) than does radiography. In early rheumatoid arthritis, MR imaging helps identify bone erosions in 45–72% of patients with disease of less than 6 months duration, compared with 8–40% for radiography. It is also important to identify those patients with early rheumatoid arthritis in whom progressive disease is not seen, since aggressive treatment may not be required in such cases. Indeed, 82% of patients without erosions at baseline MR imaging had no radiographic erosions at 2-year follow-up.

Tenosynovitis is commonly seen in early rheumatoid arthritis of the wrists and hands. MR imaging signs of tenosynovitis include fluid in the tendon sheath, increased thickness or contrast enhancement of the tendon sheath synovium, or a combination thereof (Fig 5). If tendon sheath fluid is minimal, this may be a normal finding, however contrast enhancement of the same sheath is confirmatory of tenosynovitis.

Spondyloarthropathies involving peripheral joints, particularly psoriatic polyarthritis, may pose problems in the differential diagnosis from RA. This is especially true in cases of psoriatic arthritis without psoriatic skin lesions. Radiographic changes in psoriatic arthritis appear late compared to those on MR imaging. Unlike rheumatoid arthritis, there is usually extensive involvement of the DIP joint in psoriatic arthritis. The distribution of psoriatic arthritis within the hand can also differ from that of rheumatoid arthritis, in that two or three whole digits may be involved and the remaining ones spared, whereas in rheumatoid arthritis all MCP or PIP joints tend to be involved uniformly.

Enthesitis is inflammation at sites of bony insertion of tendons, ligaments, or joint capsules, and is the hallmark of these peripheral forms of spondyloarthropathy; in fact it is thought that most joint pathologic changes are the consequence of this inflammatory process at the enthesis. Thus, identification of enthesitis at MR imaging would suggest the diagnosis of spondyloarthropathy. MR imaging findings of enthesitis include diffuse bone marrow edema adjacent to the enthesis, as well as florid inflammatory soft-tissue changes at this site (Fig 6).

Other MR imaging findings of psoriatic arthritis include periostitis with thickening and contrast enhancement of the periostea, and bone marrow edema observed in the diaphysis of the phalanges at a considerable distance from the subchondral bone and the capsular joint entheses.

In patients with rheumatoid arthritis, bone marrow edema usually occurs adjacent to cartilage in the subchondral bone and is much less extensive than in patients with spondyloarthropathy. Synovitis is not a predominant feature in most peripheral spondyloarthropathies. Moreover, whereas extensor tendons are more often involved than flexor tendons in rheumatoid arthritis, the opposite is true in psoriatic arthritis.

A key finding that may suggest the presence of spondylarthropathy is sacroiliitis, which is not a feature of RA. Imaging of the sacroiliac (SI) joints is frequently the first investigation if spondylarthropathy is suspected. The normal SI joint is composed of an anterior inferior cartilagenous portion that shows smooth margins and a posterior superior fibrous portion that shows irregular margins (Fig 7).

The anteroposterior radiograph of the pelvis is still the initial investigation performed in suspected spondylarthropathy, and erosions, ill-defined margins, sacral-side sclerosis, narrowing or ankylosis of the SI joints are key albeit late features of the disease (Fig 8). This is particularly true if there is also hip involvement, which is present in 25% of cases.

Active inflammatory lesions in spondylarthropathy include bone marrow edema, synovitis, capsulitis, and enthesitis are best visualized on STIR, fat-suppressed T2-w, and contrast-enhanced fat-suppressed T1-w images (Fig 9-11). Bone marrow edema manifests with increased signal intensity on fat-saturated fast spin-echo T2-w or STIR images, and with enhancement on gadolinium-enhanced fat-saturated fast spin-echo T1-w images. The presence of subchondral or periarticular bone marrow edema is mandatory for the definition of sacroilitis at MR imaging.

The development of new MR sequences has revolutionized the interaction between MR imaging and...
Figure 2: Synovitis in early RA of the wrist (9 months duration). Radiography revealed small erosions of the distal radius. Axial T1-w (a) and fat-suppressed T2-w (b) MR images show extensive synovitis at the dorsal and volar aspects of the wrist (white arrows), which has intermediate signal intensity in a and intermediate to high signal intensity in b. Black arrows indicate tenosynovitis of the extensor carpi ulnaris tendon. (c) Coronal gadolinium-enhanced fat-suppressed T1-w MR image shows marked enhancement of the wrist synovitis (white arrow at left). Note the diffuse bone marrow oedema, whose area of involvement includes two small erosions of the articular margin of the distal radius (black arrows). There is also enhancing tenosynovitis in the extensor tendon compartment (white arrow at right).

Figure 3: Synovitis early rheumatoid arthritis of the wrist (4 months duration) and inconclusive radiographic findings. (a) Coronal T1-w MR image shows intermediate-signal-intensity tissue in the radiocarpal, radioulnar, and ulnocarpal joints (*). An ill-defined hypointense area in the ulnar styloid process (arrow) represents bone marrow edema. (b) Axial fat-suppressed, heavily T2-w MR image shows hyperintense tissue in the radioulnar joint cavity (*), a finding that corresponds to joint fluid. Note also the intermediate signal intensity of the synovial thickening of the volar aspect of the radioulnar joint (arrows) and of the tendon sheaths of the second to fifth extensor compartments (arrowheads). (c) On an axial contrast material-enhanced fat-suppressed T1-w MR image, the radioulnar joint cavity is unenhanced (*), a finding that corresponds to joint fluid. However, the synovial thickening seen in b is now markedly enhanced (arrows and arrowheads), a finding that corresponds to acute synovitis.

Figure 4: Erosions in early rheumatoid arthritis of the wrist (1 year duration) with normal radiographs. (a) Coronal T1-w MR image shows extensive synovitis (*), along with multiple erosions of the carpal bones, distal radius, and ulnar styloid process (arrows). Coronal (b) and sagittal (c) contrast-enhanced fat-suppressed T1-w MR images again show extensive synovitis (*), with marked enhancement of the multiple erosions (arrows) seen in a. Erosions of the distal radius and lunate bone are seen in both planes.

In summary, MR imaging has revolutionised the management of RA and spondylarthropathy in that it allows much earlier detection of inflammatory joint changes and consequent early treatment to minimise joint damage. MR imaging, particularly with diffusion-weighted imaging and dynamic contrast-enhanced techniques, provides a quantitative assessment of the efficacy of treatment to help improve the outcome in these patients.
Figure 5: Tenosynovitis in early rheumatoid arthritis of the wrist (5 months duration) and normal radiographic findings. Axial T1-w (a), fat-suppressed T2-w (b), and contrast-enhanced fat-suppressed T1-w (c) MR images show marked tenosynovitis (arrows) involving both the dorsal extensor and volar flexor compartments and periscaphoid joint synovitis (*).

Figure 6: Proximal and distal interphalangeal joint arthritis in a patient with undifferentiated spondyloarthropathy (6 months duration) and normal radiographic findings. Coronal contrast-enhanced fat-suppressed T1-w MR image shows soft-tissue enhancement at the entheses surrounding the collateral ligaments of the proximal and distal interphalangeal joints of the fifth finger (arrows), along with mild synovitis.

Figure 7: (a) Coronal oblique fat-suppressed T1-w MR image of the normal sacroiliac joint shows the smooth and parallel margins of the cartilaginous lower ventral portion (arrows). (b) Coronal oblique fat-suppressed T1-w MR image obtained more posteriorly shows the irregular edges of the fibrous or ligamentous upper dorsal portion (arrows).

Figure 8: Anteroposterior radiograph of the pelvis with ankylosing spondylitis shows total ankylosis (fusion) of both sacroiliac joints (arrows) and uniform narrowing of the hip joints (arrowheads).

Figure 9: Coronal oblique fat-suppressed T2-w MR image of the sacroiliac joints in a patient with ankylosing spondylitis shows bilateral periarticular bone marrow edema (arrows).

Figure 10: Inflammatory sacroiliitis and spondylodiskitis. Coronal oblique fat-suppressed T1-w MR images obtained before (a) and after (b) the administration of paramagnetic contrast medium show marked irregularity and several erosions of both sacroiliac joints (arrows in a, white arrows in b), as well as a large erosion on the superior S1 endplate (arrowhead). Note the enhancement of the synovial portion of both joints (black arrows in b), a finding that is consistent with synovitis, and the enhancement of the S1 endplate erosion.

Figure 11: Capsulitis and enthesitis in ankylosing spondylitis. Coronal oblique (a) and axial oblique (b) contrast-enhanced fat-suppressed T1-w MR images show enhancement of both anterior capsules (arrowheads) consistent with anterior capsulitis; enhancement of the ligamentous portion of both sacroiliac joints (arrows in a), consistent with enthesitis, along with enhancement of the right facet joint (white arrow in b); and endplate erosions (black arrow in b).
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References
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