NEWSPAPERPOST

TheSynapse

The Medical Professionals' Network

Issue 03/13

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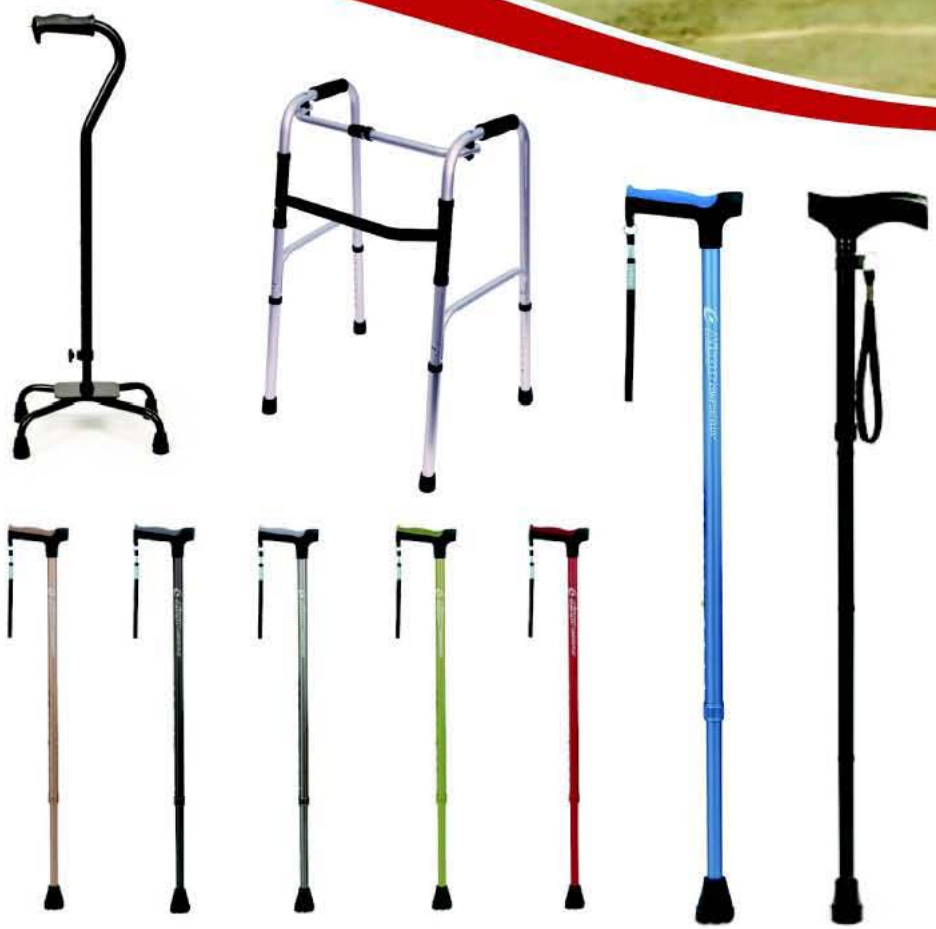

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Remedium universalis

A decade ago, the completion of the Human Genome Project was completed. This has sparked optimism that cures for debilitating diseases were within reach. But here we are, starting to organise trips to the moon and yet we have still not managed to find a universal silver bullet technique ... a medicinal product which possesses efficacy, safety and selectivity with minimal side-effects ... rather than guided missiles, today's medicines seem more like cluster bombs!

When it comes to the side-effect profile there are however some exceptions to this. These include Doxil® which was initially authorised twenty years ago in the US for the treatment of Kaposi's sarcoma. It basically enveloped the active ingredient in a liposome which in turn was impregnated with a hydrophilic polyethylene glycol (PEG) layer. However the technology still lacked one important aspect of drug delivery ... selectivity. Nowadays researchers are looking at ways in which the active ingredient, following encapsulation in a biodegradable polymer which delays the release of the drug, is surrounded with a PEG layer which has an outer layer of targeting antibodies. Since the polymer envelope is made up of more than one single component (unlike liposomes) it is possible to alter its constitution, thus modulating the release of the active ingredient. Furthermore, the inclusion of the targeting antibodies adds selectivity to the whole process. Obviously this technique holds the key for the future ... theranostics.

There are also technological innovations taking placing in parallel, which also prove to be equally interesting. An example is the development in 2012 of a screening test which enables doctors to test a tumour sample for 280 different genetic mutations suspected of causing tumour growth. The test, launched a year ago by Foundation Medicine Inc (US) has yielded surprising results. For example, in one recent case, a woman suffering from advanced pancreatic cancer tested positive for Her-2, an alteration associated with a HER-2 positive breast tumour! She was subsequently treated effectively with Herceptin®.

Other recent medical advances are also being observed in mobile technology. The AliveCor Heart Monitor® has been developed by AliveCor (www.alivecor.com) and authorised by FDA (US) as an iphone add-on which allows doctors to carry out an ECG almost anywhere. It basically consists of a case, costing €150, which snaps onto an iPhone, with electrodes on the back. It is able to record, display, store, and transfer single-channel ECG rhythms.

On the other hand, CellScope (www.cellscope.com), a mobile health company based in San Francisco, developed the CellScope Otoscope®. This is a special case featuring a protruding head, which attaches itself over an iPhone. This enables doctors to perform ear examinations using the iPhone, after which the images can be analysed using the cellscope application. Similar technologies include the iExaminer®, consisting of an iPhone Ophthalmoscope (developed by Welchallyn, www.welchallyn.com); an iPhone blood pressure monitor (developed by Withings, www.withings.com); an iPhone digital stethoscope (developed by Thinklabsmedical, www.thinklabsmedical.com); and MobiUS SP1®, consisting of a hand-held ultrasound probe transducer (developed by MobiSante, www.mobisante.com). In the latter case the use of the device is not limited to iPhones. Hopefully more devices which can be used for different types of smartphones are developed!

Ian C Ellul

A JOKE A DAY KEEPS THE DOCTOR AWAY

Who to call... the Proctologist or the Ophthalmologist?

A man with a glass eye had been out for a night on the town. Being very drunk, when he stumbled into bed, he dropped his glass eye into his drinking water on the bed table. During the night, he drank the water and swallowed the eye.

A day or so later he was suffering from severe constipation, so he went to his family doctor. The doctor inserted his proctoscope and muttered under his breath, "Good grief, I've looked up plenty of buttocks before, but this is the first one to ever look back at me."

GALVUS and EUCREAS
COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

NEW

GALVUS® is indicated as a triple oral therapy in combination with an SU and metformin[1]

EUCREAS® is indicated as triple oral therapy in combination with an SU[2]

GALVUS® and EUCREAS® indicated for use in conjunction with insulin[1,2]

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

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

Galvus®50mg (vildagliptin) tablets

PRESENTATION: Each tablet contains 50 mg of vildagliptin. **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with: metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin; a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy, in combination with thiazolidinedione, in combination withmetformin and asulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents less than 18 years old due to lack of data on safety and efficacy. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years. The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients. Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. There is no experience of vildagliptin use in clinical trails in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or lactation since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.**INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). *Monotherapy:* Common (>1/100 to <1/10): dizziness. Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Combination with metformin:* Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. *Combination with sulphonylurea:* Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. *Combination with Thiazolidinedione:* Common: weight increase, oedema peripheral. Uncommon: headache, asthenia, hypoglycaemia. *Combination with insulin* Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea, flatulenceFrequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions **LEGAL CATEGORY:** POM **PACK SIZES:** 7, 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 003. **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 124, Valletta, VLT 1000, Malta. Tel +356 22983217. 2012-MT- GAL-05-Nov- 2012.

Eucreas® (vildagliptin/metformin hydrochloride) film-coated tablets

PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS**: Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III IV and therefore use is not recommended in these patients Metformin is contraindicated in patients with heart failure, therefore Eucreas is contraindicated in this population. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. *Vildagliptin Monotherapy:* Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Metformin monotherapy:* Very common (>1/10) Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. *Combination vildagliptin with metformin:* Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. *Combination with metformin and sulphonylurea: Common:* hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:**POM PACK SIZES: 30, 60 film-coated tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002–003, EU/1/07/425/008-009.**Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 124, Valletta VLT 1000, Malta. Tel +356 22983217 2013-MT-EUC-18-Feb-2013

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Galvus® vildagliptin

Eucreas® vildagliptin/metformin

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

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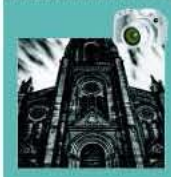

COVER:
Ghajnsielem Church
Ghajnsielem Church, Gozo by Dr Charles Paul Azzopardi. Dr Azzopardi is a haematologist at Mater Dei Hospital, with an interest in haemato-oncology. Monochrome photography provides the calming outlet to show the true, everlasting character of the subject, providing contrast between the imposing majesty of the architecture of the and the ever-grinding, ongoing motion of time. In matters photographic, the artist is entirely self-taught.

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- ✔ A good overall safety and tolerability profile
- ✔ 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 maleate, and separate Onbrez Breezhaler inhaler. **INDICATIONS:** For maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** Recommended dose is the inhalation of the 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 clinical benefit with regard to breathlessness, particularly for patients with severe COPD. Maximum dose is 300mcg once daily. No dose adjustment required in elderly patients, for patients with mild and moderate hepatic impairment or for patients with renal impairment. No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. If a dose is missed, the next dose should be taken at the usual time the next day. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** *Asthma:* Onbrez breezhaler should not be used in asthma. *Paradoxical bronchospasm:* If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. *Deterioration of disease:* Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. *Systemic effects:* Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. *Cardiovascular effects:* Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes. In case such effects occur, treatment may need to be discontinued. *Hypokalaemia:* Beta,-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. *Hyperglycaemia:* Inhalation of high doses of beta,-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 studies, clinically notable changes in blood glucose were generally more frequent by 1.2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. *Pregnancy and Lactation:* No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Immediate hypersensitivity reactions have been reported after administration of Onbrez Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Onbrez Breezhaler should be discontinued immediately and alternative therapy instituted. **INTERACTIONS:** Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists.Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS:** The most common adverse reactions with Onbrez Breezhaler are: dizziness, nasopharyngitis, upper respiratory tract infection, sinusitis, , headache, , cough, , rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. Common: Chest Pain, Oropharyngeal pain including throat irritation, Uncommon: Myalgia, Musculoskeletal pain, Pruritis/rash, Paradoxical bronchospasm, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia ,paraesthesia, atrial fibrillation and non-cardiac chest pain, ischaemic heart disease. Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. **LEGAL CATEGORY:** POM. **PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 007. **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 124, Valletta, VLT 1000 Malta. Tel: +356 22983217/+35621222872 - 2012-MT-ONB-02-Aug-2012

References:
1. Cazzola M, Matera MG. Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol. 2008;155:291-299.
2. Novartis Europharm Ltd. Onbrez® Breezhaler®. Summary of Product Characteristics.

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indacaterol inhalation powder

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Pricing of pharmaceuticals

Although the pricing of pharmaceuticals may be considered to be rather confusing, it is important to understand that this depends on several factors:

Drug development costs

It is estimated that it costs 1 billion US dollars to bring a drug to market, with the estimate rising to 4 billion US dollars if we take into consideration the cost of the drugs that fail during the pre-marketing phases and thus never make it to the market.

The availability of drugs in various markets

Although the cost of drug development is a finite cost, the ability of companies to recover the cost in various markets varies. Those countries which introduce the drugs soon after they gain a marketing authorization may be in a better position to get reduced prices as the pharmaceutical companies have a longer time to recover the expenses. In the most recent Patient's WAIT (Patients Waiting to Access Innovative Therapies) benchmarking analysis, which was conducted in 14 European countries, the duration for the introduction of 114 products ranged 88-392 days. As for the number of drugs introduced in these counties, the availability ranged 39-86%. Malta was not one of the countries that were surveyed. *Unfortunately in Malta the reimbursement of innovative drugs is very much delayed; in some cases the drug is only introduced on the government list once the patent has expired.* Thus to make the innovative drugs available to the patients in Malta many companies launch the product on the private market. However the uptake is usually very small (it is estimated that < 1% of patients opt to purchase drugs for chronic diseases, rather than take what is given for free). The low volume of sales is reflected in the price and usually this is higher than in those countries where the product is part-financed by the government.

The government purchases the drugs that are distributed through the POYC, by tender. Once the patent expires, the price of the generic versions of the drugs are a fraction of the price of the originator. In most health systems the money saved from purchasing generic drugs is reinvested in purchasing innovative drugs. *PRIMA is encouraging that local health authorities do the same.*

Size of population

Orphan drugs are obviously going to be more expensive, since in many instances expensive specialized technologies are used to develop the drugs, which ultimately result in a limited amount of revenue.

Payment of drugs

In most EU countries there is a holistic system whereby drugs bought in private retail pharmacies are included in a reimbursement system. In Malta the system is different since there are two separate markets: the private market where the patient pays the full price of the drugs, and the public market which is wholly financed by the government.

Pricing in different countries

To make sure that the innovative drugs can be afforded by all countries, pharmaceutical companies do not set a fixed price. Prices in the US and Japan are usually more expensive than in European countries. There are also discrepancies in Europe. This 'tiered pricing' is however creating problems, example, countries such as Spain and Italy have implemented price cuts to meet the strict TROIKA criteria in order to be eligible for financial aid from the EU. This is leading to a parallel trade out of these countries, which in turn is causing drug shortages in these countries. *Although 'free movement of goods' has been advocated by the EU for the past 50 years, the pharmaceutical industry is asking that parallel trade is temporarily suspended until the financial crisis is under control.*

Duration of patent and data exclusivity

The duration of a patent for chemical entities is 10 years and this starts to expire as soon as the chemical entity is registered. If one eliminates the development period, the remaining period is usually < 6 years. The cost of development has to be recovered during this time.

Reference pricing

This is the practice whereby the health authorities of countries compare the prices in other countries to establish a price that they are willing to pay for the purchase of the drug. For drugs that are given for free, the Maltese government compares the prices in a set of countries which have a GDP +/- 20% with respect to the Maltese GDP.

Technology used to produce the drugs

Today research is moving away from solid dosage forms and moving towards the development of biological treatments. These treatments are generally derived from natural products and are more costly to produce. They usually have to go through many processes to purify the product, and capacity of production is limited. S

Haemorrhoids - Epidemiology, risk factors, clinical features and management

MARCO GRECH

Anatomy and physiology

Haemorrhoids are one of the most common anal disorders encountered in primary care. Haemorrhoids are defined as the symptomatic enlargement and distal displacement of the normal anal cushions.[1] These cushions are usually found in three main locations: left lateral, right anterior, and right posterior (3, 7 and 11 o'clock positions).[2] These vascular cushions participate in the drainage of the anal canal. It has also been suggested that these cushions intensify the action of the anal sphincter mechanism, thereby contributing to continence.

There are two types of haemorrhoids: internal and external. Internal haemorrhoids arise above the dentate line, are viscerally innervated and therefore painless. External haemorrhoids can be painful because they originate below the dentate line and have a somatic innervation.[3] Internal haemorrhoids are further subdivided according to the degree of prolapsed (table 1).

Epidemiology and risk factors

Studies on the prevalence of haemorrhoids are rare and have varying results. Johnson and Sonnenberg estimated a prevalence of 4.4% in US adults, peaking in those aged 45-65 years.[5] Riss et al. in a study of 976 patients attending for colorectal cancer screening found that 38.93% suffered from haemorrhoids.[6] Only half of these reported symptoms.

Factors that increase intra-abdominal pressure are thought to contribute to the development of haemorrhoids. These include prolonged straining[1], inadequate fibre intake[2], prolonged lavatory sitting[2], constipation[1], diarrhoea[7], ascites[2] and pelvic space-occupying lesions.[2] Constipation and prolonged straining also increase the shearing force on the anal cushions, further predisposing to the formation of haemorrhoids.[1] In addition, pregnancy predisposes women to haemorrhoids, however these usually resolve after delivery.[3]

Clinical Features

Patients frequently present with painless rectal bleeding. Many treat the initial symptoms without recurring to medical advice and only present when symptoms worsen. Other symptoms may include a painful mass, anal swelling, discharge, discomfort, soiling, hygiene problems and pruritus ani. External haemorrhoids are more often associated with anal discomfort because of engorgement. If thrombosis of external haemorrhoids occurs, this causes acute pain. On the other hand, internal haemorrhoids become symptomatic when they prolapse, thrombose, bleed or become ulcerated.

Differential diagnosis includes other causes of these symptoms. It includes colorectal cancer, anal cancer inflammatory bowel disease, anal condylomata, anal fissure, perianal abscess, skin tags, perianal Crohn's disease, rectal prolapse and fistulas.

Definite diagnosis relies on an accurate history and a careful clinical examination which should include a digital rectal examination and anoscopy in the left lateral position.[1] A complete evaluation of the colon is recommended in the following clinical scenarios:[8]

- Iron deficiency anaemia;
- Positive faecal occult blood test;
- Age ≥ 50 years with no complete colon evaluation within 10 years;
- Age ≥ 40 years, with positive family history for a single first-degree relative with adenoma or colorectal carcinoma diagnosed at age < 60 years and no complete examination within 10 years;
- Age ≥ 40 years, with positive family history for two or more first-degree relative with adenoma or colorectal carcinoma diagnosed at age < 60 years and no complete examination within 3-5 years;
- Any history or physical finding indicating malignancy or inflammatory bowel disease.

Management

The management of haemorrhoids depends on the degree and severity of symptoms and it ranges from dietary and lifestyle modification to radical surgery.

(a) Dietary and lifestyle modification

An increase in dietary fibre and oral fluids may help eliminate straining during defacation thereby reducing the damage caused by the shearing action of passing hard stool on the anal mucosa. Alonso-Coello et al.[9] in a meta-analysis of seven randomised clinical trials (RCTs) of symptomatic patients, confirmed the beneficial effect of fibre in the treatment of symptomatic haemorrhoids for relieving overall symptoms such as bleeding, pain, prolapsing and itching.

Table 1: Classification of internal haemorrhoids[4]

Grade	Definition
Grade 1	May bleed but do not protrude
Grade 2	Protrude with defecation but reduce spontaneously
Grade 3	Protrude but can be manually reduced
Grade 4	Permanently prolapsed

Phlebodia 600mg

Pure diosmin

Venous insufficiency

- Relieves DURABLY[1]:
  Long lasting action proved
- Relieves PAIN: -56.1%[2]
  NEW DATA on 1 442 patients
  Decrease in pain intensity of venous insufficiency at 4 weeks of treatment
- Relieves NIGHT and DAY symptoms: 68% to 81%[2]
  Improvement or disappearance for all symptoms measured at 4 weeks of treatment

1 tablet per day every morning[3]

Haemorrhoidal crisis

- Relieves PAIN, SWELLING and/or ŒDEMA: -80%[4]
  Statistically significant difference *versus* placebo (p=0.017)
- Stop of BLEEDING in around 3 days[5]
- Patient SATISFACTION: 92%[6]
  Patients satisfied or very satisfied at the end of treatment

2 - 3 tablets per day during meals[3]

Optimal dosage:
600 mg of pure diosmin

DURABLY ACTIVE ON **NIGHT** & **DAY** **SYMPTOMS**[2]

QUICKLY ACTIVE ON **HAEMORRHOIDAL** **SYMPTOMS**[4,5]

QUALITATIVE AND QUANTITATIVE COMPOSITION: Anhydrous and pure diosmin (under the form of granulated diosmin): 600 mg. Excipients: For a core: microcrystalline cellulose, talc, colloidal silica and stearic acid. For a coated tablet: protective film (hypromellose, microcrystalline cellulose and macrogol 400 stearate), colouring mixture (propylenglycol, hypromellose, titanium dioxide, red iron oxide, black iron oxide and ponceau 4 R aluminum lacquer), purified water and Opaglos 6000 (carnauba wax, beeswax and gum lacquer). **PHARMACEUTICAL FORM:** Film-coated tablet. **CLINICAL PARTICULARS:** Therapeutic indications: - Improvement of the symptoms of venolymphatic insufficiency: heavy legs, pain, primo-decubitus restlessness. - Treatment of symptoms related to acute haemorrhoids. - Complement treatment of capillary fragility. Posology and method of administration: Oral use. Venous insufficiency: 1 tablet a day, in the morning before breakfast. Acute haemorrhoids: 2 to 3 tablets a day, to be taken before meals. Contra-indications: This drug is generally not recommended during lactation (cf. Pregnancy and lactation). Special warnings and precautions for use: Acute haemorrhoids : the administration of this product does not exempt from the specific treatment of the other anal diseases. The treatment should be of short duration. If the symptoms are not resolved quickly, a proctological examination should be performed and the treatment should be revised. Pregnancy and lactation: *Pregnancy:* animal studies have not demonstrated any teratogenic effects and no harmful effects on the foetus have been reported in man to date. *Lactation:* In the absence of data about the passage into breast milk, PHLEBODIA is not recommended during breastfeeding. Undesirable effects: Occasional cases of gastrointestinal disorders rarely requiring discontinuation of treatment. **PHARMACOLOGICAL PROPERTIES:** Pharmacodynamic properties: - Venotonic and vasculoprotective agent : it induces venous constriction, an increase in vascular resistance and a reduction of vascular permeability. - Venous myotonic. These properties have been demonstrated in various animal models and in clinical studies. **Animal studies** *Venotonic properties:* - Increase of venous pressure in the anaesthetised dog after IV administration. *Vasculoprotective properties:* - Action on capillary permeability, anti-oedematous and anti-inflammatory action in rats. - Action on erythrocyte deformability measured by erythrocyte filtration time. - Increased capillary resistance in vitamin P deficient rats and guinea-pigs. - Reduction of bleeding time in vitamin P deficient guinea-pigs. - Reduction of the capillary permeability induced by chloroform, histamine and hyaluronidase. **Clinical studies** *Venotonic properties demonstrated in clinical pharmacology:* - Diosmin increases the vasoconstrictor action of epinephrine, norepinephrine and serotonin on superficial veins of the hand or on the isolated human saphenous vein. - Increase of venous tone, demonstrated by measurement of venous capacitance using strain gauge plethysmography. - Reduction of venous stasis. - Dose-related venoconstrictor effect. - Reduction of the average venous pressure (superficial and deep system) demonstrated by a double blind test vs. Placebo under Doppler control. - Increase in systolic and diastolic blood pressure in post surgical orthostatic hypotension. *Vasculoprotective properties:* - Dose-related increase in capillary resistance. Pharmacokinetic properties: Using Carbon 14 labelled diosmin in animals it was possible to demonstrate: - Rapid absorption 2 hours following oral administration. The peak concentration was reached at the 5th hour. - Limited distribution with the exception of the kidneys, liver, lungs and especially the vena cava and saphenous veins, in which the levels of radioactivity detected were always higher than those in other tissues. This preferential binding of diosmin and/or its metabolites to venous tissue increases until the 9th hour and persists for 96 hours. - Mostly urinary elimination (79%), but also faecal (11%) and biliary (2.4%) excretion, with demonstration of an enterohepatic cycle. These results therefore indicate that diosmin is well absorbed following oral administration. Preclinical safety data: Non-clinical data reveal no special hazard for humans based on studies of acute toxicity, repeated dose toxicity, genotoxicity and toxicity to reproduction. **PHARMACEUTICAL DATA:** Shelf life: 2 years. Nature and contents of container: PVC/aluminium blister containing 15 tablets. Box of 1 or 2 blisters. Not all pack sizes may be marketed. **MARKETING AUTORISATION HOLDER:** LABORATOIRES INNOTHERA, 22, avenue Aristide Briand, 94110 ARCUEIL, FRANCE. **MARKETING AUTORISATION NUMBER:** MA617/00101. **DATE OF FIRST AUTORISATION/RENEWAL OF THE AUTORISATION:** 11th August 2006. **DATE OF REVISION OF THE TEXT:** March 2012.

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Besides increasing dietary fibre, other lifestyle modifications may play a role in the treatment or prevention of haemorrhoids. These include reducing fat consumption, regular exercise, improving anal hygiene, avoiding straining and reading on the toilet, and avoiding medication that causes constipation or diarrhoea.[1]

(b) Medical Treatment

Oral flavonoids

Oral flavonoids are thought to work by increasing venous tone, reducing venous capacity, decreasing capillary permeability, facilitating lymphatic drainage and by exerting an anti-inflammatory effect. Flavonoids have been used in a number of conditions including chronic venous insufficiency, lymphoedema and haemorrhoids.

A Cochrane systematic review by Perera et al.[10] analysed twenty four RCTs, enrolling a total of 2344 patients, evaluating the use of phlebotonics (including flavanoids and synthetic compounds i.e. calcium dobesilate) in treating haemorrhoidal disease. Phlebotonics demonstrated a statistically significant beneficial effect for the outcomes of pruritus (OR 0.23; 95% CI 0.07 to 0.79) (P=0.02), bleeding (OR 0.12; 95% CI 0.04 to 0.37) (P=0.0002), bleeding post-haemorrhoidectomy (OR 0.18; 95% 0.06 to 0.58)(P=0.004), discharge and leakage (OR 0.12; 95% CI 0.04 to 0.42) (P=0.0008) and overall symptom improvement (OR 15.99 95% CI 5.97 to 42.84) (P< 0.00001), in comparison with a control intervention. Although beneficial they did not show a statistically significant effect compared with a control intervention for pain (OR 0.11; 95% CI 0.01 to 1.11) (P=0.06), pain scores post-haemorrhoidectomy (SMD -1.04; 95% CI -3.21 to 1.12) (P= 0.35) or post-operative analgesic consumption (OR 0.54; 95% CI 0.30 to 0.99)(P=0.05) [OR – Odds ratio; SMD – Standardized mean difference; CI – Confidence interval].

Alonso-Coello et al[11] conducted a meta-analysis aimed at evaluating the impact of flavonoids on those symptoms considered to be important to patients with symptomatic haemorrhoids. The authors included fourteen published or unpublished RCTs comparing any type of flavonoids to placebo or no therapy, in patients with symptomatic haemorrhoids. These fourteen trials randomized 1514 patients. Meta-analyses using random-effects models suggested that flavonoids decrease the risk of not improving or of persisting symptoms by 58% (RR 0.42; 95% CI 0.28 to 0.61) and showed an apparent reduction in the risk of bleeding (RR 0.33; 95% CI 0.19 to 0.57), persistent pain (RR 0.35 95% CI 0.18 to 0.69), itching (RR 0.65 95% CI 0.44 to 0.97) and recurrence (RR 0.53 (95% CI 0.41 to 0.69)). This meta-analysis is, however, limited by the important heterogeneity present for all the outcomes, and by the potential of publication bias as there was a failure to identify additional unpublished studies with small or absent treatment effects, thereby possibly overestimating the true effect of treatment.

Topical treatment

Topical treatment aimed at controlling the symptoms of haemorrhoids can contain local anaesthetics, corticosteroids, and anti-inflammatory drugs in the form of creams and suppositories. Many of these preparations help to alleviate symptoms of pruritus and discomfort. However, there are no randomized trials suggesting a reduction in bleeding or prolapsing. Caution should be used when prescribing corticosteroid-containing local preparations, since although they improve local perianal inflammation, their prolonged use can cause thinning of the perianal skin.[12]

(c) Non-operative treatment

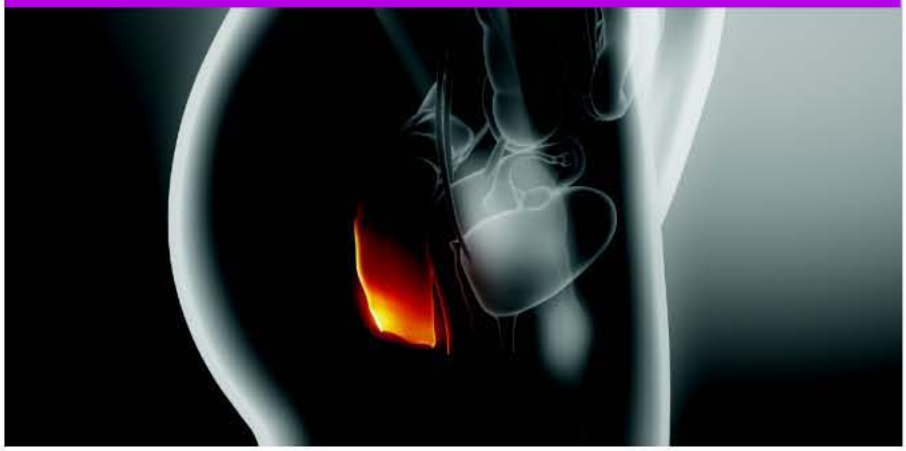
Sclerotherapy

Sclerotherapy is recommended as a treatment for Grade 1 and 2 haemorrhoids.[13] Sclerotherapy involves the injection of chemical agents to create a fixation to the underlying mucosa by fibrosis.[13] Possible complications of this procedure include transient precordial and upper abdominal pain,[14] mucosal ulceration or necrosis and, rarely, prostatic abscess or retroperitoneal sepsis.[15] Antibiotic coverage is indicated in patients with predisposing valvular disease or immunodeficiency.[16]

Rubber band ligation

Ligation of the haemorrhoidal tissue with a rubber band causes ischemic necrosis, ulceration and scarring, leading to fixation of the connective tissue to the rectal wall. The rubber bands are placed above the dentate line. Complication rates are low and include vasovagal attacks and persistent anal pain.[17] Other reported complications include late haemorrhage (1-2 weeks after the procedure),

The most effective treatment for haemorrhoids with the lowest rate of recurrence compared to other treatments is haemorroidectomy



thrombosed external haemorrhoids, ulceration, slippage of the rubber band, pelvic sepsis and, very rarely Fournier's gangrene.[18-20] The risk of delayed bleeding makes rubber band ligation contraindicated in patients on anticoagulants.

Infrared coagulation

This procedure involves the application of radiation to the base of the haemorrhoid causing coagulation, occlusion and sclerosis of the haemorrhoidal tissue. The scarring that ensues reduces blood flow to the haemorrhoid. Success rates of infrared coagulation are lower than those of rubber band ligation[21] but it can safely be offered to those on anticoagulant therapy.[2]

(4) Operative treatment

Haemorrhoidectomy

The most effective treatment for haemorrhoids with the lowest rate of recurrence compared to other treatments is haemorroidectomy.[22] An elliptical incision over the haemorrhoidal complex is done, the haemorrhoidal complex is then mobilized from the underlying sphincter and subsequently excised. The wound is then sutured.[2] Indications include failure of non-operative management, strangulation or thromobosis of haemorrhoids, concomitant anorectal conditions e.g. anal fissure or fistula, and patient preference.[23]

Complications of haemorrhoidectomy include post-operative pain[24], acute urinary retention, post-operative bleeding, septic complications, wound breakdown, delayed wound healing, loss of anal sensation, prolapsing of the mucosa, anal stricture, and fecal incontinence.[25]

A Cochrane review of three RCTs by Shanmugam et al.[26] comparing excisional haemorrhoidectomy to rubber band ligation showed ligation to be associated with less post-operative pain. Excisional haemorrhoidectomy was also associated with overall greater individual complication rates but there was no statistically significant difference in the incidence of urinary retention, haemorrhage and anal stenosis. Patient satisfaction was similar in both groups. Excisional haemorrhoidectomy in patients with Grade 3 haemorrhoids resulted in less symptom recurrence and a reduced need for subsequent procedures. The authors concluded that rubber band ligation can be considered to be the treatment of choice for Grade 2 haemorrhoids while excisional haemorrhoidectomy should be reserved to Grade 3 haemorrhoids or following recurrence after rubber band ligation.

Stapled haemorrhoidopexy

In stapled haemorrhoidopexy a circular device excises a ring of redundant rectal mucosa proximal to the haemorrhoid and resuspends the haemorrhoid back within the anal canal interrupting the blood supply to the haemorrhoidal tissue.[27] Post-operatively, patients have a circular staple line above the dentate line. Post-operative pain is less than with excisional haemorrhoidectomy but there is a higher risk of recurrent haemorrhoids.[28,29] Stapled haemorrhoidopexy is mainly reserved for patients with circumferential prolapsing haemorrhoids and those having ≥ 3 lesions of advanced internal haemorrhoids.[1]

Conclusion

The treatment of haemorrhoids depends on the degree and severity of symptoms. It includes dietary and lifestyle modifications, medical treatment such as flavonoids and topical treatment and, where indicated, surgical treatment. S

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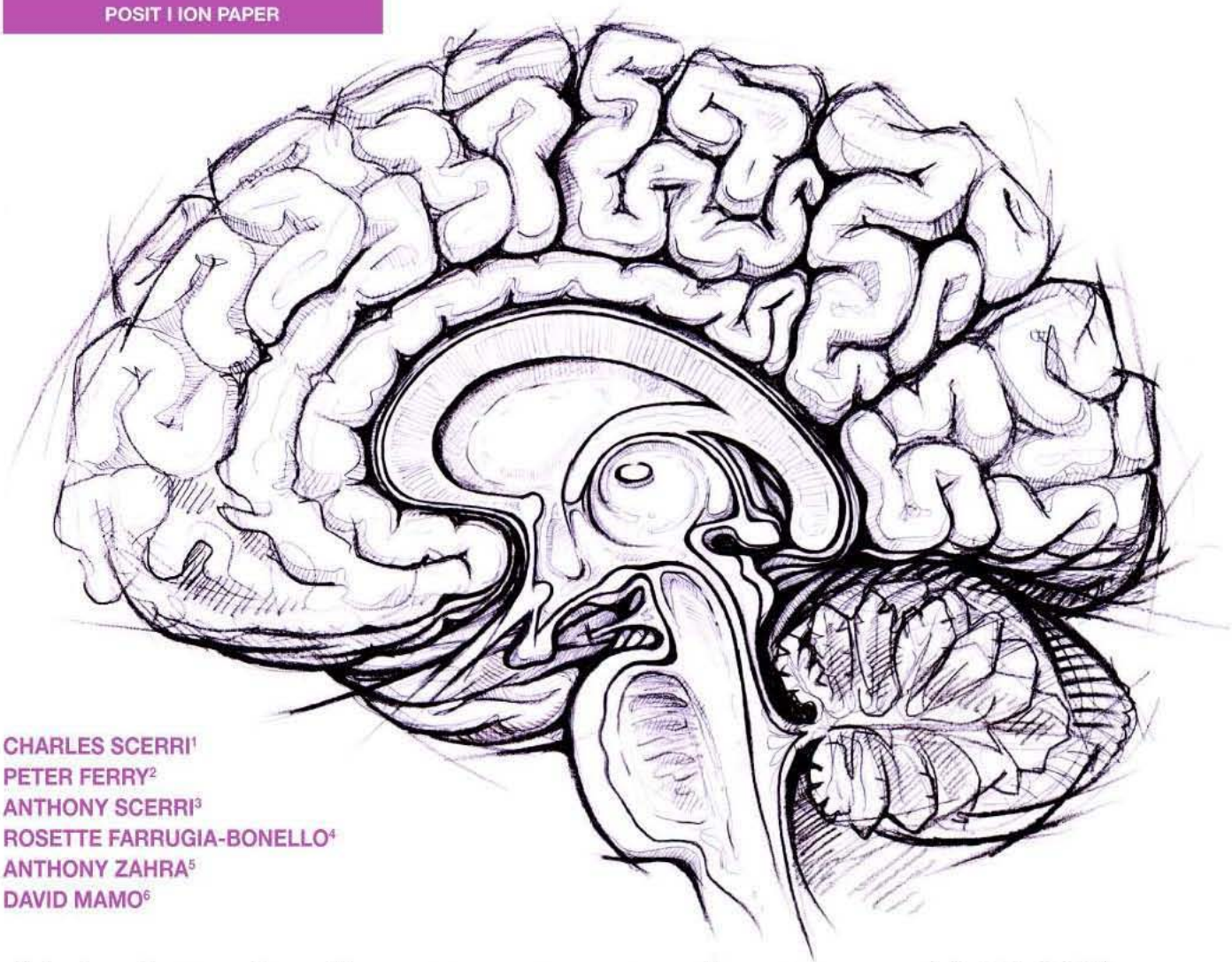

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Alzheimer's disease research group (ADRG)

Introduction

In these last few years, there has been a growing consensus in Europe and beyond on the need of increasing research on neurodegenerative diseases including Alzheimer's disease and other related dementias. The societal impact and financial consequences of these diseases are already being felt and will continue to grow with the projected rise in the elderly population. Currently, there are over 35 million individuals with dementia worldwide, a figure that will treble by the year 2050. It has been estimated that formal and informal dementia care costs a total of €445 billion (2009 data),[1] equivalent to 1% of the global gross domestic product. It is therefore not surprising that the European Union supports various funding programmes in the hope of enhancing diagnosis, provide better treatment and improve care pathways and support for individuals with dementia, their caregivers and relatives.

Alzheimer's disease

Approximately 50% to 70% of all dementia cases are of the Alzheimer type. Alzheimer's disease, first identified in 1907 by the German neurologist Alois Alzheimer, is a progressive neurodegenerative disorder characterised by the presence of plaques and tangles in areas of the brain controlling cognitive function. Symptoms include memory impairment, difficulties in spatial orientation, changes in mood and personality, communication deficiencies and functional losses in activities of daily living. As the disease progresses, cognitive function becomes more impaired and individuals will eventually become totally dependent on others. Life expectancy following diagnosis varies but usually ranges between 8 to 15 years. Risk factors include age, female gender, presence of Apo4 gene, repeated head trauma and cardiovascular and metabolic factors. There is no single test to determine the presence of Alzheimer's disease and diagnosis relies on several features including the elimination of other co-morbidities, careful physical and mental examination, clinical investigation and disease progression.

Dementia in Malta

Particular interest in the field of dementia in Malta kicked off with the launch of the Malta Dementia Society in September 2004. The main aim of the society is that of increasing awareness on dementia in the Maltese islands through the organisation of seminars and talks on various aspects of dementia care and management. The Malta Dementia Society is an active member of Alzheimer Europe and Alzheimer Disease International and is frequently invited to participate in various European and pan-European initiatives. The first study to determine the prevalence of dementia in the Maltese islands was published in 2007.[2]

The findings estimated that, in 2010, there would be approximately 4,500 individuals with dementia, accounting to 1.1% of the local population. This figure is expected to double in the next 30 years. Recent data on prevalence rates using new criteria suggests that the number of individuals with dementia is higher than previously reportedand should exceed 14,000 cases by the year 2060.[3] This progressive increase in affected individuals will have important socio-economic consequences and will invariably put greater demands on government-supported health care services. Moreover, there will be a growing burden on family members who, in the majority of cases, provide informal care at home.[4] The importance of addressing this increasing phenomenon led to the setting-up of the Malta Dementia Strategy Group in 2009 with the aim of presenting a series of recommendations to the Ministry of Health that should enhance high-quality dementia care.[5] The final document laying down the backbone of the National Dementia Plan was presented in January of 2010. Although the final text have not been published to date, various recommendations included in the plan are being ratified such as the addition of dementia among the chronic conditions listed in the Schedule V of the Social Security Act.

Dementia Research in Malta

Although financial resources have been limited, research on dementia including Alzheimer's disease in Malta has increased considerably in these last five years. Most of this research is based at the University of Malta and focuses on cellular, molecular, pharmacological and social aspects of dementia with special emphasis on Alzheimer's disease. Following a grant funded by the Malta Council of Science and Technology (Research and Innovation Programme 2008-2012) to study how naturally occurring compounds can act as possible protective agents in Alzheimer's disease, a number of contributionswere published in international peer-reviewed journals.[6-8] Publications in other areas of Alzheimer's disease and related dementias include those by Innes et al,[4] Scerri,[5] Scerri et al[9] and Scerri and Scerri.[10] A number of local and international undergraduate and graduate students have also been involved in the running of this research programme.

Alzheimer's Disease Research Group (ADRG)

The number of students interested in furthering their research in dementia is progressively increasing. Furthermore, Alzheimer's disease is becoming a topic of national interest and the number of research projects in which Malta is expected to act as a partner is expected to grow in the future. Albeit its size and geography, Malta can have an important voice as demostrated by the number of requests to collaborate in various foreign-based projects. With this in mind, the Department of Pathology has launched the Alzheimer's Disease Research Group with the aims of:

1. Bringing together a number of multidisciplinary professionals in the field of Alzheimer's disease and related dementias;
2. Promoting and facilitating research and scientific collaboration in the diverse disciplines in Alzheimer's disease and related dementias with the ultimate goal of improving patient and caregiver care and quality of life;
3. Acting in unision with local dementia NGOs in the dissemination of scientific knowledge and advancement of research goals in Alzheimer's disease and related dementias;
4. Participating in and exploring local and international research funding proposals in the basic, social and clinical fields of Alzheimer's disease and related dementias.

A number of international research institutions have already shown interest in forming workable partnershipswith this group both in national, European and pan-European funded projects. It is hoped that through such research cooperations, the University of Malta will continue on its endevour of becoming an important contributor in the field of Alzheimer's disease research.

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MASSIMO AZZOPARDI

When cooking builds teams

As a matter of fact, food brings people together. We have all experienced at least one occasion where food was being served, shared, displayed, cooked, sold, bought, delivered or prepared.

Cooking can be exciting in itself especially when shared in groups. I have had several opportunities to cook for family, friends and groups out of my professional line of work and found it to be very exciting when I involved the invitees. Depending on the space available, equipment and cooking experience, one can decide who will do what during the exercise.

As a catering and events consultant, I have also applied this sort of coming together to corporate clients and organisations requiring an event that will stimulate their workforce. Cooking in groups does not only build the team but enhances better understanding and communication. The interaction created through cooking and food preparation gets everyone on the job to focus on the end result, the meal. It enhances barrier breaking while it stimulates teamwork through problem solving techniques. One can share recipes, cooking methods and family traditions, at times also originating from other countries.

The interactivity created during a group cooking session delivers good results of positiveness with that "let's do it" attitude. The final result can also motivate the team further when dining together, during which they have the opportunity to discuss the food cooked which does not necessarily need to be up to a professional culinary level.

There are several outcomes from cooking sessions, not simply learning how to cook. When applied as a team-building event, participants will learn more about others, and also on how to overcome obstacles, resolve issues, take different roles and above all create fun that can elevate their own (and their company's) performance.

Win a meal for two at the Tarragon Restaurant in St Paul's Bay

One of our members is currently reading for a Masters degree in Public Health Medicine at the UOM. The thesis is entitled "Beliefs and attitudes on antibiotic use in Malta: Informing Intervention Strategies." The objective of the study with prescribers is to find out about attitudes on antibiotic prescribing in Malta and how best to inform campaigns for the general public to improve knowledge and awareness. The response by prescribers will be very useful to the outcome of this study and therefore we would like to thank you in advance for taking time to participate. The survey may be accessed through the following link: **http://tinyurl.com/hv-antibiotic.** Should you have any problems or queries you may contact Helen Vella on **hvel0004@um.edu.mt.** **Participants will also have the chance of winning a meal for two at the Tarragon Restaurant in St Paul's Bay.**

During August 2-9th 2013, Dr Pierre Vassallo and Ms Kathleen Schembri from DaVinci Hospital will venture to climb the highest mountain in Africa, Mt Kilimanjaro in Tanzania. Kilimanjaro is almost 6000 meters high and reaching the peak is not for the faint hearted.

We are fully financing this trip ourselves, however we decided to use the occasion to collect funds to construct a home for disabled children in Ethiopia; this is the Cardinal Van Thuan Home in the province of Jimma. All funds collected through this effort will be channeled towards construction of this home through NGO VO/0140. There will be no deductions made to cover any expenses incurred on our trip.

Advances in general surgical laparoscopy

Jo Etienne Abela MD FRCS FEBS MPhil
Consultant General and Laparoscopic Surgeon

Introduction

Minimally invasive surgery has been with us for the past century. The last thirty years have seen an exponential growth in the development of laparoscopic techniques which allow major surgery to be performed through smaller incisions and less trauma leading to enhanced recovery and earlier discharge from hospital.

Diagnostics

Diagnostic laparoscopy may be performed through 3 sub-centimetre incisions, allowing an accurate exploration of the peritoneal cavity. It has changed the management of the acute abdomen and the staging of upper gastrointestinal cancer. In the former setting, laparoscopy may be employed to make a confident diagnosis of appendicitis, Meckel's diverticultitis, terminal ileitis, tubal and ovarian pathology, bowel ischaemia and visceral perforation. These conditions may be dealt with primarily by laparoscopy. In the oncological setting, low volume liver and peritoneal disease which is not readily identifiable by CT and PET, may be encountered. In these scenarios tumour upstaging will avoid unnecessary major surgery.

Biliary surgery

Laparoscopic cholecystectomy has now been performed for a few decades and was largely the primer to the development of most other laparoscopic operations. Aside from being the standard of care for the cold calculous gall bladder, it is fast becoming the treatment of choice (during the index admission) for the patient with acute biliary colic, acute cholecystitis and mild biliary pancreatitis. Intra-operative cholangiography may be performed with relative ease obviating the need for MRCP and ERCP. If bile duct stones are confirmed, laparoscopic bile duct exploration and clearance may be offered to provide a single-stage laparoscopic management.

Hernia surgery

Laparoscopic surgery has been successfully employed in the reconstruction of all forms of herniae. The totally extra-peritoneal approach (TEP) may be used for inguinal, femoral, obturator and Spigelian defects. Recurrent and bilateral defects are particularly suited to this approach. Intra-peritoneal techniques lend themselves well for the repair of large umbilical and incisional herniae, avoiding the otherwise large incisions which are associated with protracted pain and a high incidence of infection. Laparoscopy has revolutionalised the management of hiatal hernial defects. The sliding hernia associated with GORD may be treated with a crural repair and fundoplication. Large rolling (para-oesophageal) herniae containing stomach (Figure 1), but on occasions bowel and spleen, may be reconstructed with or without recourse to prosthetic implants (Figure 2). Heller's myotomy for achalasia (with or without an anti-reflux procedure) is now also routinely performed.

Resectional surgery

Virtually, every abdominal and pelvic organ may be excised by laparoscopy. Splenectomy (Figure 3 and 4), adrenalectomy, nephrectomy and colectomy are now being performed on a routine basis. In tertiary level centres hepatic, pancreatic and oesophago-gastric resections are still the province of the enthusiast.

Figure 1: CT images showing gastric volvulus in a rolling hiatal hernia (hS:herniated stomach, S:obstructed stomach, d:diaghragm).

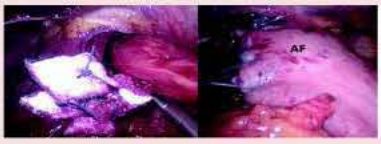

Figure 2: Completed crural repair using PTFE pledgets. AF:anterior fundoplication.

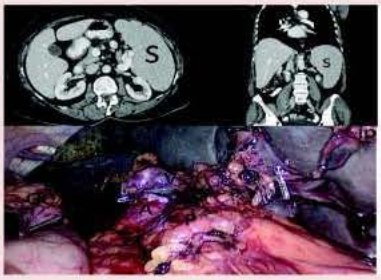

Figure 3: CT images of splenomegaly due to marginal zone lymphoma. GC:greater curve of stomach, A:splenic artery, P:tail of pancreas, V:splenic vein, ip:inferior pole of spleen)

Figure 4: Patient in Figure 3. The 25cms spleen was morcelated and delivered through a 3 cm incision in the left loin.

The use of novel anticoagulants in non-valvular atrial fibrillation

ANDREW CASSAR

Atrial Fibrillation (AF) occurs in 1-2% of the general population, making it the commonest sustained cardiac arrhythmia. It becomes more common as one gets older, with a prevalence of 5-15% at 80 years of age. Atrial fibrillation is independently associated with doubling of mortality, mostly associated with a higher risk of stroke. One-fifth of strokes are due to AF, with a proportion of 'cryptogenic' also likely to have undiagnosed AF as a cause. Anti-thrombotic therapy is the only treatment which reduces deaths in patients with AF.[1]

The increased risk of stroke is present in all patients with AF, and no difference exists between patients with paroxysmal or permanent AF. However, numerous risk factors are independently related to an increased risk of thrombo-embolic disease. These risk factors include previous strokes/ transient ischaemic attacks/ thrombo-embolic episodes, age, diabetes, hypertension, congestive heart failure, structural heart disease, and gender. Risk-stratification tools, notably $CHADS_2$ and CHA_2DS_2-VASc scores (Table 1), have been created in order to better score and quantify the adjusted stroke rate for a given patient. A CHA_2DS_2-VASc score of 2 would confer a 2.2% yearly adjusted risk of stroke, while with a score of 6 the risk would go up to 9.8%.[1,2]

Over 2 decades ago, numerous large multi-centre trials have shown that Vitamin-K Antagonists (VKA) significantly reduce the risk of stroke when compared to placebo with a relative risk (RR) reduction of 64%.[3] The anti-coagulant effect of VKAs is mediated by blocking the production of Vitamin K-dependent coagulation factors II, VII, IX and X. Starting a patient on anti-coagulation therapy, however, is not without risks. The increased risk of bleeding, especially gastro-intestinal and cerebral bleeds, are dreaded complications. A balance between the patient's risk of stroke and his/her risk of bleeding has also to be taken into consideration.[1,3]

Studies comparing thrombo-embolic prophylaxis with aspirin versus VKA all showed significant superiority of the latter. In fact, the efficacy of aspirin in preventing stroke in AF is doubtful, as many studies comparing it to placebo failed to show a significant reduction of stroke. The few studies which showed a positive outcome for aspirin had their methodology heavily criticised. Notwithstanding, aspirin is still considered by some as an option in AF patients with no or a single stroke risk factor.[1]

Thrombo-embolic prophylaxis with VKA, with warfarin being the most common, has been at the forefront in the management of AF patients. VKA therapy is fraught with many problems, mainly related to inter- and intra-patient variation in their pharmacological effect. The anti-coagulation effect of VKAs, measured using INR, is dependent on a patient's genetic makeup and associated with significant drug, alcohol and food interactions. Patients therefore cannot be given a 'standard dose' and need to get frequent INR testing, with the dose being adjusted accordingly. In 'real-life' situations, over half of the time, patient on VKA are under-coagulated, and therefore are not getting the intended therapeutic benefit.

Table 1: CHA_2DS_2-VASc score adapted from the European Society of Cardiology guidelines for the management of AF[1]

Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)		**Adjusted stroke rate according to CHA_2DS_2-VASc score**		
Risk Factor	**Score**	**CHA_2DS_2-VASc score**	**Patients (n=7329)**	**Adjusted stroke rate (%/year)**
Congestive heart failure/Left Ventricular dysfunction	1	0	1	0%
Hypertension	1	1	422	1.3%
Age >75	2	2	1230	2.2%
Diabetes mellitus	1	3	1730	3.2%
Stroke/TIA/thrombo-embolism	2	4	1718	4.0%
Vascular disease	1	5	1159	6.7%
Age 65–74	1	6	679	9.8%
Sex category (i.e. female sex)	1	7	294	9.6%
Maximum score	**9**	**8**	**82**	**6.7%**
		9	**14**	**15.2%**

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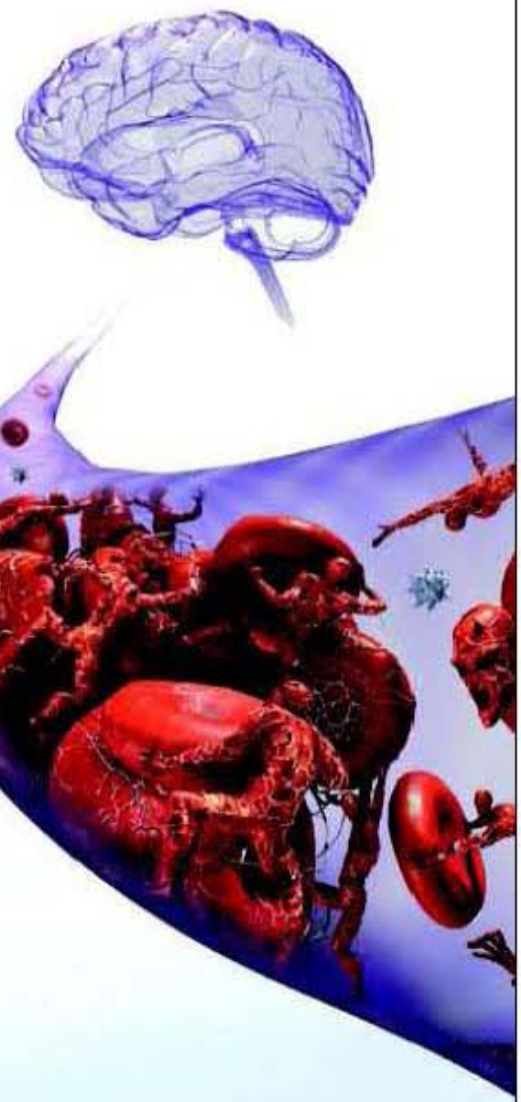

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[a]Per-protocol, on-treatment analysis. Event rate: Xarelto (1.7%/yr) vs warfarin (2.2%/yr), $P<0.001$ for non-inferiority.

[b]Fewer intracranial haemorrhage events: Xarelto (0.5%/yr) vs warfarin (0.7%/yr), $P=0.019$. Fewer fatal bleeding events: Xarelto (0.2%/yr) vs warfarin (0.5%/yr), $P=0.003$.

Patients on Xarelto had significant increases in the following major bleeding events: a ≥2 g/dL fall in haemoglobin (2.8%/yr vs 2.3%/yr, $P=0.019$) and transfusions (1.7%/yr vs 1.3%/yr, $P=0.044$).

Mucosal bleeding events were seen more frequently with Xarelto compared with warfarin.

Xarelto® 15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)
Presentation: 15mg/20mg rivaroxaban tablet **Indication(s):** 1. Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). 2. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *Dosage 1 (SPAF):* 20 mg orally o.d. with food. *Dosage 2 (DVT & PE):* 15 mg b.i.d. for 3 weeks followed by 20 mg o.d. for continued treatment & prevention of recurrent DVT & PE, take with food. Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment necessary; moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29 ml/min, limited data indicates rivaroxaban plasma concentrations are significantly increased, use with caution) – SPAF: reduce dose to 15mg o.d., DVT & PE: 15 mg b.i.d. for 3 weeks, thereafter 20mg o.d. Consider reduction from 20mg to 15mg o.d. if patient's bleeding risk outweighs risk for recurrent DVT & PE. Patients with creatinine clearance <15 ml/min - use not recommended. ***Hepatic impairment:*** Do not use in patients with hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications:** Hypersensitivity to active substance or any excipient; clinically significant active bleeding; lesion or condition at significant risk of major bleeding (refer to SmPC); concomitant treatment with any other anticoagulant agent except under the circumstances of switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain a patent central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings & precautions:** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. Following sub-groups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation. Use with caution - in patients with severe renal impairment or with renal impairment concomitantly receiving potent inhibitors of CYP3A4 (PK models show increased rivaroxaban concentrations); in patients treated concomitantly with medicines affecting haemostasis. Use is not recommended in patients with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. If invasive procedures or surgical intervention are required stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established. See SmPC for full details. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as increased rivaroxaban plasma concentrations to a clinically relevant degree are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** Adverse reactions like syncope (uncommon) & dizziness (common). Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious:* cf. *CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, abnormal hepatic function, hyperbilirubinaemia, jaundice, vascular pseudoaneurysm. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **MA Number(s):** EU/1/08/472/011-21 **Further information available from: Alfred Gera and Sons Ltd,** Telephone: 210446205. Date of preparation: June 2013
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Many patients who, despite being on VKA therapy, develop thrombo-embolic episodes are in fact found to be inadequately anti-coagulated. Warfarin and other VKAs also have a long half-life and therefore pose a problem when emergency surgery is needed.[1]

Novel Oral Anti-Coagulants (NOACs) have recently become available, as a 'non-VKA' alternative, for thrombo-embolic prophylaxis in non-valvular AF patients.[4,5] What these drugs share in common is that they block a single step in the coagulation cascade. Three drugs are currently approved by the European commission for the prevention of stroke in patients with non-valvular AF: the direct thrombin-inhibitor dabigatran (Pradaxa®, Boehringer Ingelheim), and the direct factor Xa inhibitors rivaroxaban (Xarelto®, Bayer) and apixaban (Eliquis®, Pfizer/ Bristol-Myers Squibb). These 3 NOACs have been accepted as an alternative to VKAs on the strength of the results obtained in 3 clinical trials comparing them to warfarin. The RE-LY trial compared 2 different dabigatran doses (110mg and 150mg twice daily) to warfarin, the ROCKET-AF trial compared warfarin to rivaroxaban 20mg once daily, while ARISTOTLE compared warfarin to apixaban 5mg twice daily. These trials followed earlier trials which had shown success for NOACs in preventing venous thrombo-embolic events (VTE) in patients undergoing orthopaedic surgery.

The RE-LY trial was an open-label trial comparing dose-adjusted warfarin to a randomised dose of either 110mg or 150mg of dabigatran.[6] In this trial, dabigatran 150mg was superior to warfarin for the occurrence of stroke and systemic embolism, with no significant difference in major bleeding. Dabigatran 110mg was on the other hand non-inferior to warfarin, but with 20% fewer major bleeds. Rates of haemorrhagic stroke and intracranial haemorrhage were lower with both doses of dabigatran, but gastrointestinal bleeding was significantly increased with the 150mg dose. There was a non-significant numerical increase (28%) in myocardial infarction (MI) with both dabigatran doses. A meta-analysis of 7 dabigatran trials (including VTE prophylaxis trials) was carried out because of the concern of the small increase in myocardial infarctions.[7] Despite a 33% significant increase in MI, an 11% reduction in all-cause mortality was seen when compared to warfarin. The increased risk of MI with dabigatran is thought to be due to the protective effect of warfarin, rather than being caused by the new direct thrombin inhibitor.[8]

Rivaroxaban was approved for the prevention of stroke in non-valvular AF following the randomised double blinded ROCKET-AF trial.[9] This study showed that rivaroxaban 20mg once daily (reduced to 15mg in patients with renal failure) was non-inferior to warfarin, on an intention-to-treat basis, for the primary end-point of stroke and embolic episodes. Although the rates of mortality and ischaemic strokes were similar, patients on rivaroxaban had significantly less haemorrhagic strokes and intracranial haemorrhages.

The latest drug approved for anti-coagulation in non-valvular AF is apixaban, which was approved on the strength of the ARISTOTLE trial.[10] In this study 5mg twice daily apixaban (with dose reduction to 2.5mg in renal failure, > 80yrs, or < 60kg) was compared to warfarin in a randomized, double-blind, double-dummy manner. Apixaban showed superiority to warfarin with a 21% reduction in stroke and systemic embolism, a 31% reduction in major bleeding, and an 11% reduction in all-cause mortality.

The lack of head-to-head trials between different NOACs makes it inappropriate to make direct comparisons. The 3 major trials had different populations, with slightly different inclusion and exclusion criteria resulting in different baseline characteristics. For example, the ROCKET-AF trial had an older population with a higher $CHADS_2$ score than the other 2 trials. All drugs have some renal excretion (with 80% in dabigatran) and therefore all NOACs need to have their dosage reduced in renal failure. To date, there is no specific antidote to reverse their anticoagulant effects in case of emergencies; however they all have short half-lives. From a compliance point of view, rivaroxaban has the distinct advantage of being a once daily dose. As time goes by, NOACs will also find new indications, as seen by the recent EMA approval of rivaroxaban for acute coronary syndromes.

The recent launch of oral non-Vitamin K anticoagulants heralds a new era in stroke prophylaxis of non-valvular AF patients. In the next few years they will surely replace warfarin which, despite its effectiveness, is frowned upon for its cumbersome dosing regimen by both patients and clinicians. S

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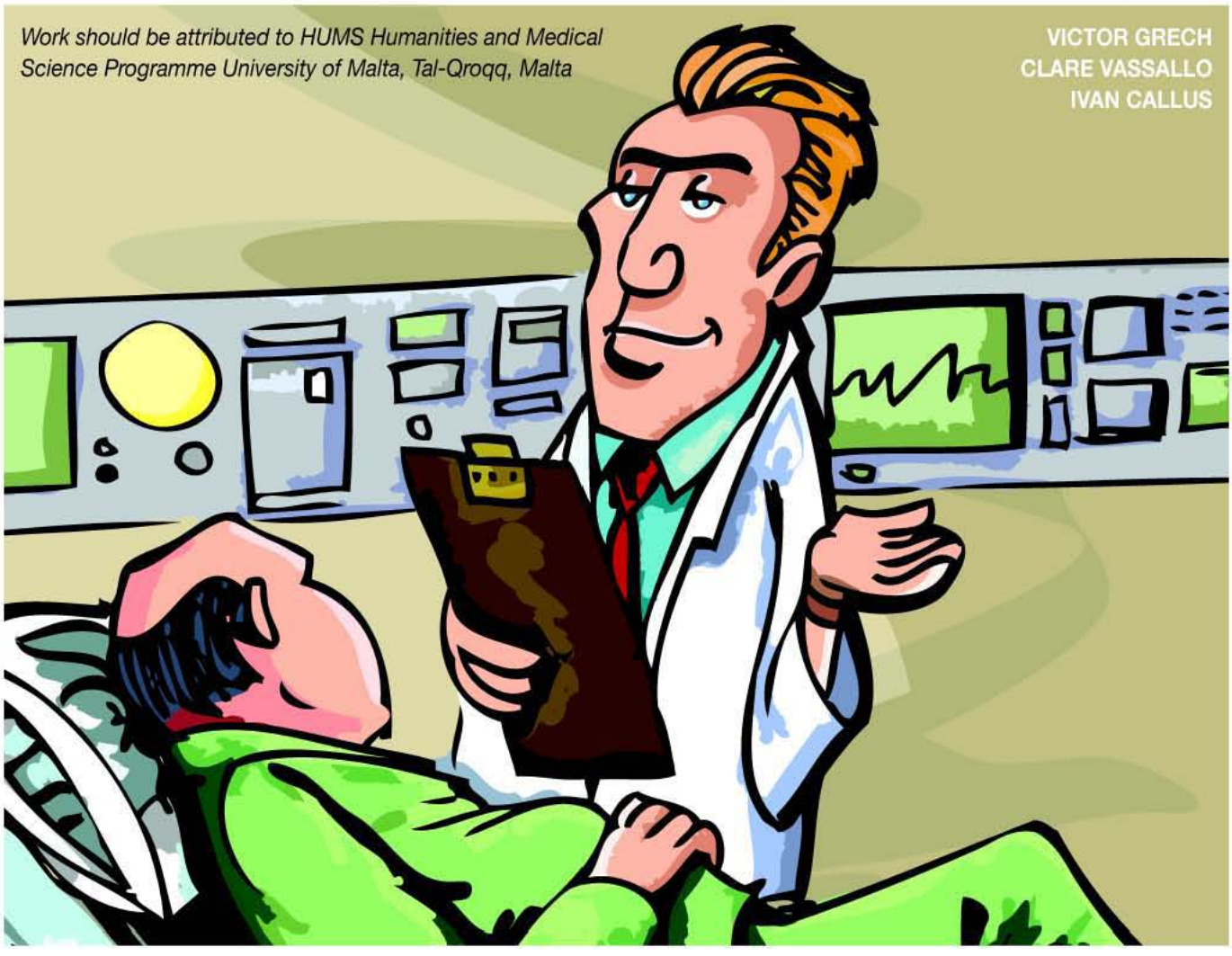

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VICTOR GRECH
CLARE VASSALLO
IVAN CALLUS

MEDICINE FOR THE SOUL

relations between Medicine & Humanity

The human condition provides a common ground between medicine and literature as doctors and writers both witness and share in the passion and tragedy of human existence, particularly when death and disease intervene. Both doctors and writers are also inextricably involved in the outcomes of these struggles, hence the attempt to stand back and retain objectivity may not always succeed. Similarly, doctors and writers document the events and milestones that befall individuals, doctors in history taking and writers in life stories. It is therefore not at all surprising that the relationships, contacts and associations between medicine and literature are many, varied, and as old as the Greeks. Indeed, 'Medicine for the Soul' was inscribed above the door to the library at Thebes in Ancient Egypt (c. 3000 BC). Conversely, Epicurean rhetoric and Greek empiricism were discussed by Hippocrates, the father of medicine. Moreover, medicine itself necessarily invites attention by posing a glaring internal contradiction as embodied in James Bryce's words, medicine is 'the only profession that labours incessantly to destroy the reason for its own existence'.[1]

Medicine has indubitably exerted a strong influence on literature with many writers having a sound layman's knowledge of the subject matter or a strong medical interest or contact with doctors, and a non-comprehensive list includes Daniel Defoe, George Eliot, Charles Dickens, Alexander Solzhenitsyn, Thomas Mann, and Peter Shaffer. The extreme is for the author to actually have had medical training, and such individuals include Thomas Browne, Tobias Smollet, Oliver Goldsmith, Johann Wolfgang von Goethe, John Keats, Arthur Conan Doyle, Anton Chekhov, Oliver Wendell Holmes, Robert Bridges, William Somerset Maugham, William Carlos Williams, Richard Seltzer, Gertrude Stein, Arthur Schnitzler and Oliver Sacks. Such authors inherently have tremendous insight in humdrum, everyday doctor-patient interactions and manage to imbue such events with interest.

The converse may also be true, and doctors who immerse themselves in the humanities may make better

physicians, an assertion that is put forward in Rita Charon's *Narrative Medicine: Honoring the Stories of Illness* (2006).[2] Charon contends that doctors should appreciate that illness is not just an encounter with a disease but is often also a problem arising out of a particular lifestyle, for instance, the two commonest examples of risky lifestyles are promiscuity and exposure to drugs, both of which have been linked to infertility, as already discussed.[3]

It is abundantly clear to medical practitioners that in order to make the individual whole, the psychological aspect of the patient is as important as the physical, an approach that was advocated as far back as Hippocrates and Galen, who also realised that a patient's outlook to life often also affects the course and ultimate prognosis of a disease. The value of recognising the effects of mind over body in healing has also long been recognised, for example, in Burton's *Anatomy of Melancholy* (1621), which propounded the theory that knowledge of psychology is one of mankind's greatest needs. Burton believed that melancholy was responsible for exaggerated moods, such as the passion and despair of lovers, the ecstasies of the religious and the frenzies of madmen.[4] Therefore the questions arise: Should doctors just doctor or should they be involved in research, act as counsellors and philosophers and generally function as a moral force in society? And how then have the institution of medicine and its practitioners been represented in mainstream literature?

Doctors belong to that branch of science that holds human bodies, lives, and deaths in its thrall, and are therefore highly significant figures in our lives. Fictional interpretations of doctors emphasise this as the medical profession is often portrayed in a dramatic and vivid way, with representations such as Frankenstein's monster reanimated from corpses and charnel waste. It is therefore intriguing to observe that fiction has been unexpectedly disinclined to deal with medical matters, and when it has, it has consistently displayed ambivalence, cynicism and distrust. Doctors and medicine have never been particularly fashionable subjects in mainstream literature, often non-existent in stories, and when they do occasionally appear, are hardly ever depicted as popular or heroic. For that matter, illness itself has also hardly ever been the focus of mainstream literature. A typical example is Virginia Woolf's essay *On Being Ill* (1926) who correctly states that:

[c]onsidering how common illness is, how tremendous the spiritual change that it brings, how astonishing, when the lights of health go down, the undiscovered countries that are then disclosed, what wastes and deserts of the soul [...] it becomes strange indeed that illness has not taken its place with love, battle, and jealousy among the prime themes of literature.[5]

It is worth pointing out an upsurge of interest in this topic, as evinced by a recent British Council Walberberg Seminar which was themed 'Literature and Health'. However, overall, not only are doctors in mainstream literature rarely ever main protagonists, but they are occasionally also accused of being quacks, or of being unprofessional or behaving unethically. Indeed, they may actually be portrayed as villains, either after transformation as in Stevenson's *The Strange Case of Dr. Jekyll and Mr. Hyde* (1886),[6] or through an actively corrupt and criminal nature such as Ferdinand Bardamu in Céline's *Voyage au bout de la nuit* (Journey to the End of the Night) (1932).[7] Moreover, several eminent authors have suffered significant morbidity and mortality from conditions that are eminently curable or treatable by today's medical knowledge, with chronic diseases, such as tuberculosis being the prime culprits. One example is Henley's *In Hospital* (1903) which describes his own experiences in hospital after having to have a foot amputated due to tuberculous arthritis.[8]

An excellent review on this topic is provided by Lilian R. Furst in *Between Doctors and Patients: The Changing Balance of Power* (1998),[9] a study which links popular novels with recent medical history, outlining the way in which medicine has gained credence, and confronting the psychological and philosophical motifs implied therein. Furst pleads for medicine to be more 'collaborative' with patients, joining 'the physician and his patient together in learning, teaching, communicating, and understanding'.[9] Indeed, our collective knowledge of and faith in modern medicine's powers is reflected at the individual level as although we know, intellectually, that we are not immortal, we still expect medicine and doctors, its acolytes, to somehow provide us with a series of 'endless deferrals'.[9] Such outlook is repeatedly depicted in mainstream and contemporary texts, such as Roth's *Everyman* (2006),[10] where a protagonist reinforces this aphorism when stating 'there's no remaking reality [...] just take it as it comes. Hold your ground'.

Should doctors just doctor or should they be involved in research, act as counsellors and philosophers and generally function as a moral force in society?

And since, arguably, 'in nothing do men approach so nearly to the gods as in doing good to men',[11] it is almost as if medicine is somehow perceived as a mystical entity, virtually a god, and doctors, the promulgators of medicine, akin to demigods, the writers of (usually) illegibly mystical prescriptions, and the wielders of a bewildering array of seemingly magical bullets that they utilise to influence the collision between hope and the reality of disease. The disappointment for the individual, whether patient or author, is therefore all the greater when medicine fails to provide a satisfactory cure: no fountain of youth on tap and no elixir of immortality at hand, and even more so when the doctor himself disillusions the patient, stating 'I too am mortal'. Individual doctors may therefore be perceived as healers and decision makers, knowledgeable and possessing a special craft or skill in the practice of medicine that is often referred to as an art, but are considered in turn with ambivalence; as being arrogant or compassionate, ignorant or wise, hated or admired. For all of these reasons, medicine and doctors offer an almost infinite range of material to the prospective author.

Why are doctors and medicine so often portrayed negatively in classical texts, such as Dr. Lydgate, for example, in *Middlemarch*?[12] Is it that inherent discrepancy in the fundamental approaches of doctors and authors, the anecdote? Doctors believe that 'the clinical case report is a foundational text that enables clinicians to depict, reason, and instruct others about a sick person's medical situation'.[13] This is the only form of anecdote that doctors are trained to accept, albeit warily, with more credibility given to objective evidence derived from large-scale research studies. Conversely, authors create stories, unavoidable anecdotes. Or could it be that novelists are somehow jealous of doctors and their powers? Could authors be disdainful of doctors or medical practices that occasionally fail? Or are authors resentful of the fact that in sickness, they become hopelessly vulnerable and fall helplessly and relentlessly under the control of the medical profession? This cannot be the case, at least not for doctors who are themselves writers. The more likely reason is that writers deal in contrast and paradox, in the belief that reality is best depicted through irony, satire and contradiction. The most brilliant works of fiction provide insight into the dark side of the human condition, contrasting it with instances of individual magnanimity and nobility, and this is often afforded through conflict and misunderstanding. However, the most complete understanding of human nature alone is insufficient without the exploitation of a backdrop of true life experience, and medicine is uniquely placed, by dealing with morbidity and mortality, to penetrate the interface and provide such a backdrop. This has also been acknowledged by members of the medical profession who have frequently forsaken, temporarily or even permanently, their scientific responsibilities in order to take up literary roles, sharing their perceptions and insights into health and disease, and one brief example will be given.

Anton Chekhov (1860-1904), the famous Russian author and playwright, was a practising physician who drew abundantly on his medical experience in order to provide the scenery and characters for his fictional material, imposing a dispassionate examination of human nature and of doctors who are a subgroup of humanity and are therefore subject to all of the common manifestations of human failing including ennui, cynicism, politics, greed, frailties, overwork and the consequences of burnout. In his stories, Chekhov however also reveals redeeming medical qualities of dedication, the zealous pursuit of medical knowledge, and perseverance under adverse circumstances while also exploring the issue of professional detachment in both subject and degree.

The medical profession is particularly suited to interdisciplinary ventures, such as writing fiction because of the origins of the discipline. This is because historically, the medical field commenced from a dubious set of barbers and bloodletters, and through the study of anatomy, physiology and the sciences advanced to medicine as we know it today, eager to embrace new intellectual, technical and technological advances. It is only in the last few decades that doctors have forayed into areas of social concern, including the effects on health on environmental change, pollution, war, famine, pestilence and natural disasters.

In conclusion, the medical profession is fully cognizant of its contributions to the humanities and several colleagues have attempted to showcase medicine's involvement in literature.[14] Only one example will be given, Thomas Browne (1605-82) whose *Religio Medici* (The Religion of a Doctor) became an instant European best-seller came , as it did, from a profession whose members were widely thought to have no religious beliefs.[15] The book is Browne's spiritual testament and psychological self-portrait, and its unorthodox views instantly relegated it to the Papal *Index Librorum Prohibitorum.*[16] Many have lauded Browne, and Woolf averred that this book paved the way for confessionals, memoirs and personal writings.[17]

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MARIKA AZZOPARDI

Of DNA, molecules and genetics

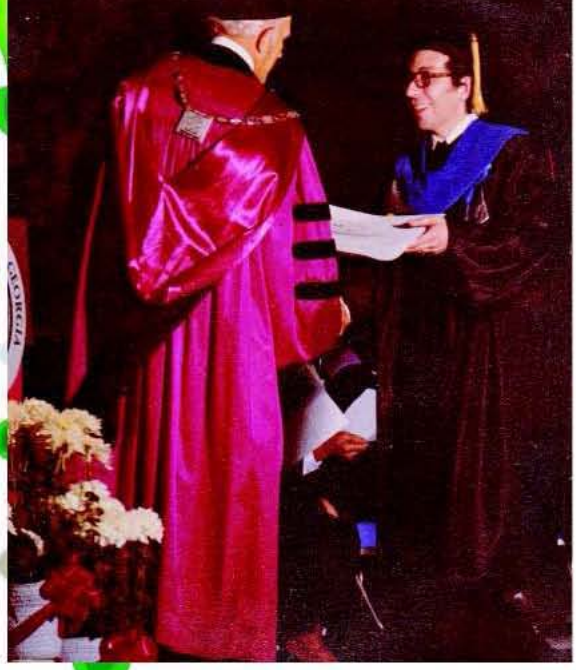
He was turning nine when the discovery of the DNA drew attention world-wide. It was the scientific discovery of the century and it would influence him definitely towards his future career choice. Alex Felice was the son of a chemist but perhaps, had the wonder of DNA not impressed him so much, he would not have taken such a strong interest in his father's profession. As things turned out, the mysteries of biochemistry had him enthralled enough to encourage him to take up medicine at University.

Professor Alex Felice is today an appreciated specialist and researcher in the field of genetics. He is known for his intensive work in the research on thalassaemia and in his research on the haemoglobin variants present in the Maltese population. He explains how all this came about, "I graduated M.D. in 1971 and during my first years at St. Luke's, I took every possible opportunity to head for the labs and work there – I preferred lab work to ward rounds any day. My mentor was the late Joe Louis Grech, the clinical pathologist at the time. When the opportunity arose to become a research fellow in William Bannister's new department, I took it on with gladness and did my Masters research on the genetics of haemoglobin and thalassaemia."

With Joana, his wife, celebrating their 25 anniversary

He eventually moved on from Malta, taking up a research position in the Sickle Cell Centre of Titus Huisman in the Medical College of Georgia, Augusta Georgia, US. At the time, it was one of two leading centres for research on haemoglobin genetics. The other was at Oxford University, run by David Weatheral. Alex gained his Ph.D in 1981 and then took on posts at the Medical Research Service of the Veterans' Administration Medical Centre as 'Principal Investigator for Haemoglobin Research' and the Faculty of the Medical College of Georgia in the School of Medicine and the School of Graduate Studies, becoming Associate Professor in 1985.

Eventually he returned to Malta and resumed work here opening a clinic and a laboratory, starting a research programme and introducing studies at Masters and Doctoral levels



Receiving his PhD from Professor William Moretz, President of the Medical College of Georgia (now Georgia Health Science University) in 1981

Receiving an award from Panos Englezos, president of the Thalassaemia International Federation at the International Thalassaemia Conference in Malta

for University students. Today his professorship has led him to continue studying the Maltese scenario and continue working with the small but dedicated team of young scientists who have trained under his guidance. "The small group of trainees who started out with me when I resumed work here, has today developed and evolved so that each has achieved great accomplishments. Christian Scerri is Professor and heads the Section of Genetics at Mater Dei Hospital and Connie Bezzina is Professor of Molecular Cardio-Genetics at the Academic Medical Center in Amsterdam, The Netherlands. John Rizzo Naudi, Peter Seracino Inglott and Dr Paul Vassallo-Agius were very supportive. Currently, we have three Masters students and two PhD students researching with us. This research is of utmost importance. Our key interest lies in the mechanisms that regulate gene expression in health and disease. It is at the tender age of approximately six months that infants complete the genetic switch from foetal haemoglobin to adult haemoglobin. Thalassaemia manifests itself at this switch-over phase. We have identified the KLF1 gene that in our opinion is the master regulator of switching. We now know that in the rare eventuality that the switch-over does not materialise in infants pre-disposed to develop thalassaemia due to their genetic make-up, thalassaemia does not manifest at all. This discovery is of utmost importance and we are seeking to find ways of controlling this switch-over phase. Joseph Borg earned his Ph.D. for this work and he is now a lecturer in our new Faculty of Health Sciences. We are collaborating with the research group led by Sjak Phillipsen at the Erasmus Medical Center in Rotterdam, The Netherlands to search for the medication to help control the switch-over" This work has resulted in the publication of nearly 70 research manuscripts, most of which in leading journals.

Another interesting aspect of his work is bio-banking. A collection of specimens has already been organised in Malta as part of a much larger research infrastructure which is being set up across Europe, namely, the Biobanking & Biomolecular Resources Research Infrastructure. This bank is seeking to achieve global inter-operability which will be very valuable for patients and families with hereditary diseases that fall within the class of orphan diseases. His group at the University of Malta is also a founder member of Euro BioBank and the research consortium on rare disease known as RD-CONNECT.

But what about Malta? How does Malta's genetic pool fare? "The novelty is that many babies seen today carry African and Asiatic traits in their genes. Whether migration is legal or illegal, it happens and it affects the genes our children carry. However, we have averaged the Maltese genome and know for certain that as expected, 95% of our genes come from Sicily and Southern Italy. The historical and archeological records are consistent with this finding. We also find quite a few genetic abnormalities that appear to be unique to the Maltese."

Professor Felice speaks with excitement about a new project which is in progress, and which will turn into a public information exercise. "In the near future we are planning to invite the public to participate and help us research our national gene pool further. This will be of immense help to our future generations and their health. I am already excited by the possibilities it will bring forth, and hope that the public will be forthcoming." S

However, we have averaged the Maltese genome and know for certain that as expected, 95% of our genes come from Sicily and Southern Italy

Imaging complications of assisted Reproductive Procedures

PIERRE VASSALLO

The incidence of assisted conception has increased dramatically in Europe, doubling over the past decade. Assisted reproductive technology (ART) is involved in approximately 1% of births in the developed world. With the increasing use of ART, doctors and radiologists are more likely to encounter associated complications that are sometimes life-threatening. These complications include ovarian hyperstimulation syndrome (OHSS), ovarian torsion, and ectopic and heterotopic pregnancy. Awareness of these entities and their imaging features will facilitate accurate and timely diagnosis and help avoid potentially fatal consequences.

OHSS is a potentially life-threatening iatrogenic complication of ovulation induction or ovarian stimulation. It occurs during the luteal phase of the menstrual cycle or in early pregnancy. Its pathogenesis involves secretion of ovarian vasoactive angiogenic substances (vascular endothelial growth factor – VEGF) by the granulosa-lutein cells of the ovary particularly under the influence of hCG, which cause increased capillary permeability and accumulation of fluid in the extravascular space. This manifests with bilateral ovarian enlargement by multiple cysts, third-spacing of fluids (i.e. ascites, pleural effusions and dependent oedema), and clinical findings ranging from gastrointestinal discomfort to life-threatening renal failure and coagulopathy (due to haemoconcentration).

OHSS is classified according to the Golan classification into mild, moderate and severe based on ultrasound and clinical findings (Table 1). The incidence of OHSS varies by stimulation regimen. Clomiphene induction is associated with rates of mild and moderate OHSS of approximately 13.5% and 8%, respectively; the severe form is rarely seen in association with clomiphene induction. Following gonadotropin stimulation (particularly hCG), the incidence of mild, moderate, and severe OHSS is 20–33%, 3–6%, and 0.1–2%, respectively.

The imaging findings of OHSS are similar on ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging i.e. bilateral symmetrically enlarged ovaries containing multiple variable-sized cystic lesions representing enlarged follicles or corpus luteum cysts, in the presence of ascites (Figure 1).The distribution of the ovarian cysts may be such as to create a spoke-wheel appearance with thin radiating septa between the cysts and a central hub of ovarian tissue (Figure 2). Haemorrhage may also occur into the cyst (Figure 3) that may result in accentuation of the pain. Similar imaging findings are seen on CT (Figure 4) and MR imaging (Figure 5).

Enlarged hyperstimulated ovaries are also at risk for torsion. The risk is further increased in the presence of ascites and pregnancy. Clinical symptoms are often nonspecific, and ovarian torsion should be suspected and excluded in any female patient undergoing infertility treatment who presents with severe abdominal pain. The most consistent imaging finding is asymmetric enlargement of the torted ovary (Figure 6). The presence of arterial and venous flow on colour Doppler US does not exclude the presence of torsion. Visualisation of the torted ovarian pedicle as the "whirlpool sign" is helpful in making the diagnosis (Figure 7). As with US, the most common finding of ovarian torsion in CT and MR imaging is unilateral ovarian enlargement (Figure 8). Prompt diagnosis of ovarian torsion is essential to prevent irreversible ischemia and infarction. Ovarian salvage is particularly important in patients who are already pregnant and in those desiring future conception.

An ectopic pregnancy is defined as an abnormally implanted embryo. In this case, the blood supply is derived from this abnormal implantation site. As the pregnancy progresses, the potential for rupture is created which could result in massive hemorrhage and death.

Table 1: Golan classification of ovarian hyperstimulation syndrome

Category	Ovarian size (cm)	Grade	Signs / symptoms
Mild	< 6cm	I	Abdominal distension
		II	Abdominal distension, nausea, vomiting, diarrhoea
Moderate	6-12cm	III	Abdominal distension, nausea, vomiting, diarrhoea, ascites on US, weight gain
Severe	> 12cm	IV	Ascites/pleural effusion
		V	Ascites/pleural effusion, hypovolaemia, haemoconcentration, coagulation disorder, oliguria, shock

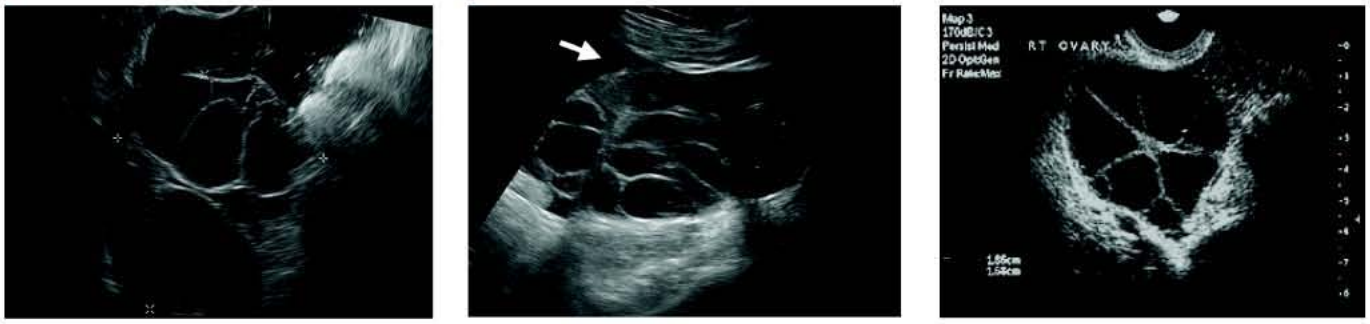


Figure 1: Transvaginal US images of the right (A) and left (B) ovaries in a case of hyperstimulation that presents with ovarian enlargement, numerous large cysts and ascites (arrow in b).

Figure 2: US showing the spoke wheel appearance of ovarian hyperstimulation.

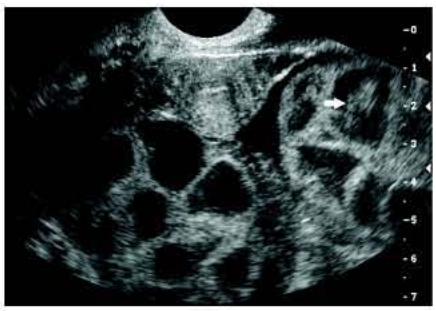


Figure 3: US showing haemorrhage (white arrow) into a cyst in ovarian hyperstimulation. Ascites (black arrow) is also present.

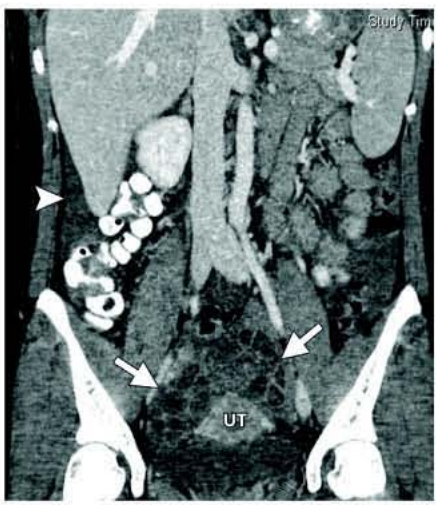


Figure 4: Coronal CT scan in a patient with OHSS shows bilateral ovarian enlargement by multiple cysts (arrows) and mild perihepatic ascites (arrowhead). Uterus (*UT*).

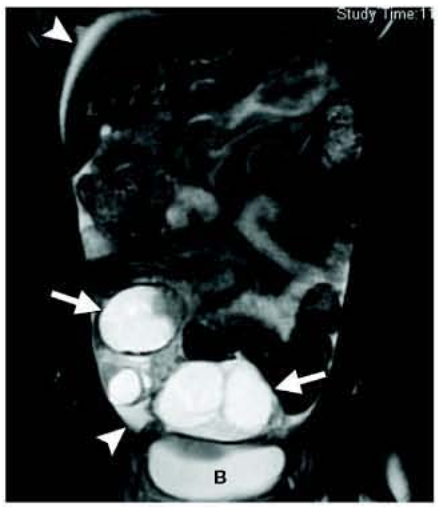


Figure 5: MR image carried out in a patient with OHSS due to clinical suspicion of appendicitis. Coronal fat-saturated T2-weighted image shows bilateral ovarian enlargement (arrows) and mild ascites (arrowhead). Bladder (*B*).

There is also an increased risk for ectopic pregnancy following ART with a reported incidence in different studies ranging from 2.1% to 8.6%. 82% of ectopic pregnancies are tubal in location; however there is a relative increased risk for rarer and more lethal forms including interstitial and cervical ectopic pregnancies.

Patients with suspected ectopic pregnancy are initially evaluated with quantitative measurement of serum β-hCG in addition to transvaginal US. In general, transvaginal US should demonstrate at least a gestational sac when serum β-hCG levels exceed 2000 mIU/ml. Absence of an intrauterine gestational sac with β-hCG levels above this threshold should raise the suspicion of ectopic pregnancy and trigger a comprehensive search. Failure of the β-hCG level to increase (doubling time of 49 hours) should also raise the suspicion of an ectopic pregnancy. Importantly, 35% of ectopic gestations do not demonstrate an extrauterine mass.

The most common finding in a tubal pregnancy is an adnexal mass separate from the ovary (Figure 9), with increased specificity when it moves independently from the ovary or contains a yolk sac or living embryo with demonstrable cardiac activity. The second most common sign of a tubal pregnancy is the tubal ring sign (Figure 10) that consists of a gestational sac surrounded by a hyperechoic ring. Similar findings may be detected by MR imaging (Figure 11), while residues of blood products in the surrounding structure may indicate ongoing rupture.

Interstitial pregnancy refers to an implanted gestational sac in the intramyometrial portion of the fallopian tube. Symptoms of such an ectopic pregnancy tend to manifest later and rupture may result in catastrophic hemorrhage due to proximity to the uterine artery. At US, an eccentrically located gestational sac surrounded by a thin layer of myometrium measuring less than 5mm may be seen (Figure 12). Cervical ectopic pregnancy is 10 times more common in ART patients and results from embryo implantation in the endocervical canal. US findings include an hourglass-shaped uterus secondary to cervical expansion (Figure 13).

US diagnosis of ectopic pregnancy is particularly challenging in women undergoing fertility treatment as there is a large degree of overlap in the signs

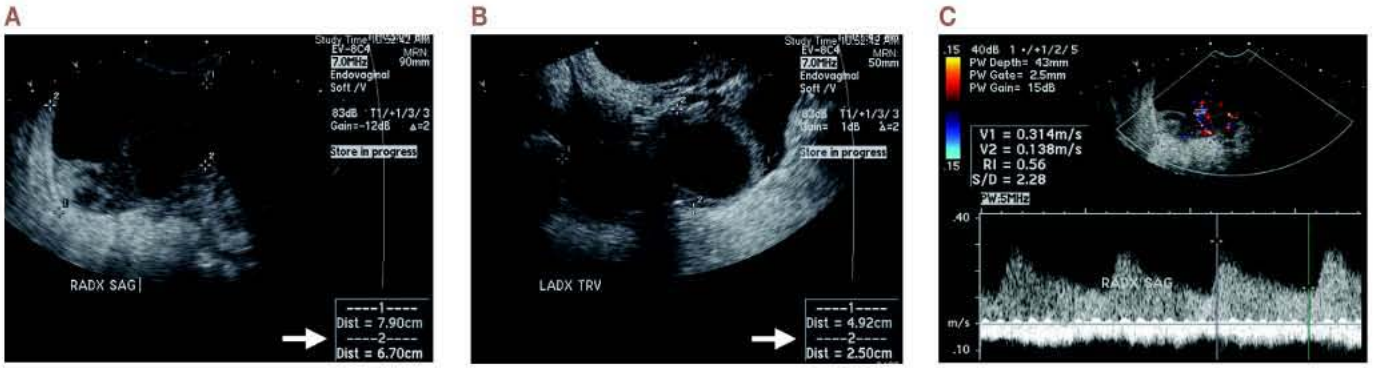


Figure 6: US images show enlarged, multicystic right **(A)** and left **(B)** ovaries consistent with OHSS. The right ovary is asymmetrically enlarged (arrow), the only clue to ovarian torsion in this case. **(C)** Duplex Doppler US image of the right ovary shows arterial and venous flow.

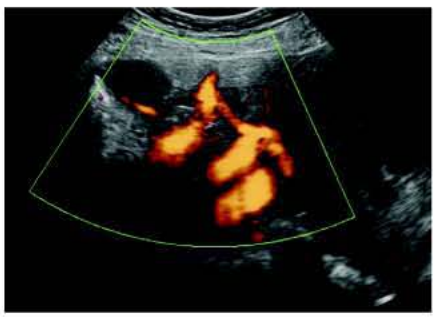


Figure 7: The "whirlpool sign" on colour Doppler US represents the torted ovarian pedicle. Notice the corkscrew appearance of the vessels.

and symptoms. Pelvic pain is common following ART, especially in OHSS. Stimulated ovaries are enlarged, which may obscure an ectopic pregnancy. Ascites is often present following ART, especially in the setting of OHSS, and hemorrhagic ascites may result from rupture of a corpus luteum cyst (rather than a rupturing ectopic gestation).

Heterotopic pregnancy refers to simultaneous intrauterine and ectopic pregnancies and has an incidence of 1–3% in ART patients. In women undergoing infertility treatment, careful evaluation of the adnexa is crucial even if an intrauterine pregnancy is documented. Ultrasonography is the first-line imaging modality for the evaluation of complications of ART, although nonspecific symptoms may sometimes lead to other cross-sectional imaging being performed. Familiarity with the multimodality imaging appearance of these entities will allow accurate and timely diagnosis and help avert potentially fatal consequences.

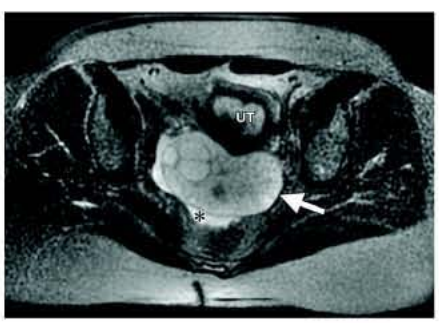


Figure 8: MR scan shows the enlarged torted left ovary (arrow) compared to the right (not seen). Also notice that the enlarged ovary tends to occupy a midline location and no longer lies along the pelvic sidewall. Ascites (*).

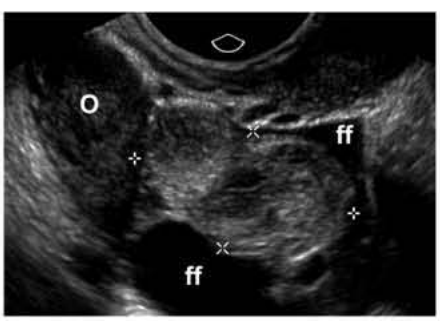


Figure 9: Endovaginal US image shows a paraovarian ectopic pregnancy as a mass (between crosshairs) adjacent to the right ovary (o) with surrounding free fluid (ff).

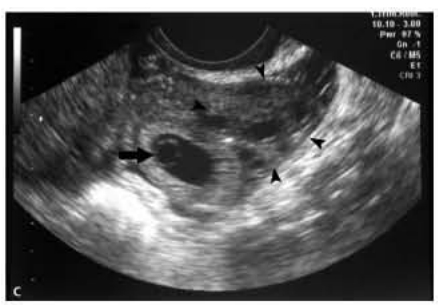


Figure 10: Endovaginal US image showing the tubal ring sign (arrow) confirming a tubal ectopic pregnancy adjacent to the normal left ovary (arrowheads).

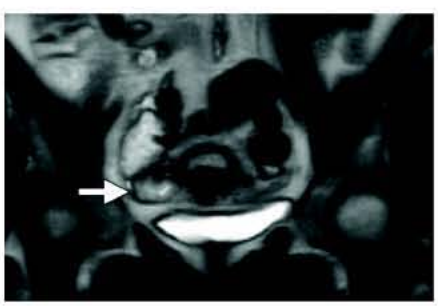


Figure 11: Coronal T2-weighted MRI image shows a tubal ring to the right of the uterus confirming a tubal pregnancy.

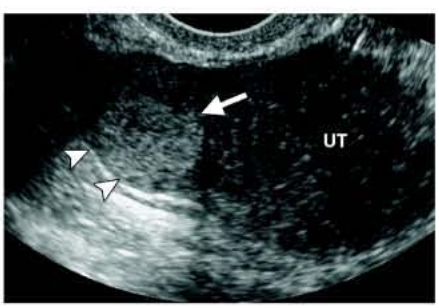


Figure 12: Endovaginal US showing a hyperechoic (haemorrhagic) gestational sac (arrow) eccentrically located in the uterine fundus with a posterior thin myometrial layer (arrowheads).

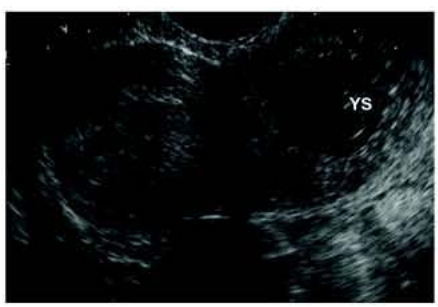


Figure 13: Cervical ectopic pregnancy with a figure eight configuration of the uterus and cervix. A gestational sac containing a yolk sac *(YS)* is seen in the cervix.

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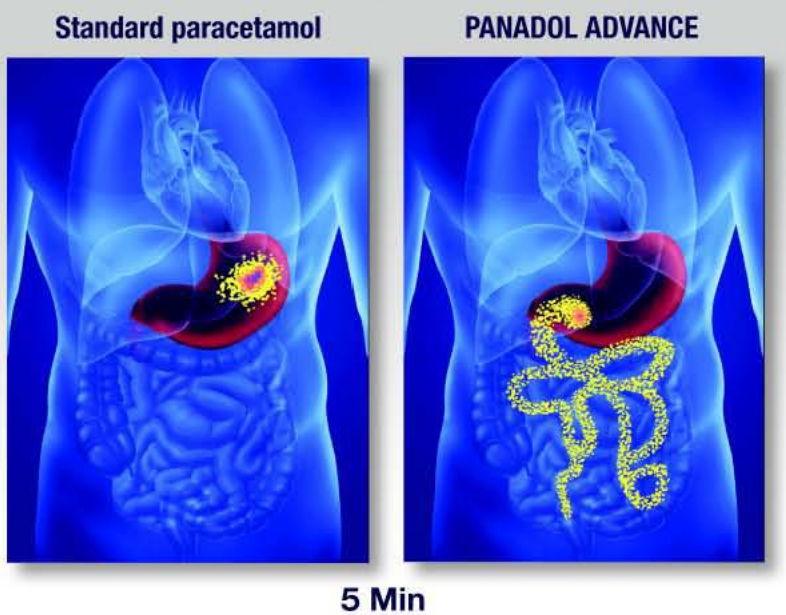

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*Representation of actual gamma scintigraphy images of paracetamol in the gastrointestinal (GI) tract.

References

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