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THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

- Meningococcal B Vaccination: A Novel Approach
- Does Education lead to Better Health?
- CVD Challenge - Win with Servier

Volume 16, 2017 Issue 02 ISSN number 2313-8084

ACTIVATE THE HEART*

ACTIVATE LIFE[1,2]

GUIDELINE† CLASS I RECOMMENDED[3,4]

Change your symptomatic HFrEF patients to ENTRESTO®

- **Activates the heart's beneficial response** by enhancing the natriuretic peptide system, while maintaining RAAS inhibition[5,6]
- **20% reduced risk** of CV death or first heart failure hospitalisation vs enalapril ($P<0.0001$; ARR=4.7%)[5‡]
- **Significant improvements in Quality of Life** vs enalapril, as measured by reduced deterioration of heart failure symptoms and physical limitations ($P=0.001$)[7§]

When you see symptoms, IT'S TIME FOR ENTRESTO[5]

Entresto®
sacubitril/valsartan

ARR=absolute risk reduction; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; RAAS=renin-angiotensin-aldosterone system.

*The complementary cardiovascular benefits of ENTRESTO in patients with HFrEF are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitril and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan.

†Based on 2016 ESC HF Guidelines and 2016 ACC/AHA/HFSA Guideline Update.

‡Primary end point.

§Secondary end point that measured the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

ENTRESTO™ v(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥ 100 mmHg. Patients with SBP < 100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. Undesirable effects: Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Frimley Business Park, Camberley, GU167SR, United Kingdom. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the 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 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2016-MT-ENT-16-JUN-2016

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THE UPCOMING MALTESE GENERAL ELECTION

PRIDE & PREJUDICE

Media has recently reported that the forthcoming Maltese election will most probably be held this year. One does not need to be an expert in history to foresee that the temperament of the government during the pre-election period will change, becoming more 'sanguine', aiming to please the greatest number of people in the shortest time possible. This will also be the case with the opposition's attitude, where one will see it gradually relinquishing its somewhat navel-gazing 'melancholic' and at times, 'choleric' attitude to embrace a similar attitude.

We always seem to experience two paradigm shifts around each election period. Apart from payments of long-standing dues by the government to private contractors and unsolicited invitations to lavish buffets by candidates, the election period always invariably coincides with collective agreement renewals. During the pre-election period, we see various unions at loggerheads with the government to improve the benefits of their union members. The most lucrative collective agreements are always spearheaded by those unions who enjoy the greatest lobbying power since they hone on the ever-present threat of industrial action. So be it!

The second paradigm shift which we experience during the pre-election period is the most creative juggling of development boundaries and building heights. ODZ approvals for relatively small construction works take place on a monthly basis all year round. However, it is only during the few months [or days] prior to the election that a 4 tumolo ODZ field, worth Euro200,000 and facing a built-up area, can become worth Euro 4,000,000, following such a development boundary tweak.

However, at this stage let us concentrate on the health sector. If I were to make a calculated guess of the pre-election war of words between the two main political parties, I would mention that, on one hand the government will boast that:

- ✓ the bleak situation of increasingly out-of-stock medication which was a monkey on the back of the Health Minister for more than a decade has been effectively solved.
- ✓ generally speaking, the waiting lists for operations have continued to decrease.
- ✓ following the 2017 budget, diabetic patients in possession of the schedule V card [yellow card] have started benefiting *again* from free dental care, subsidies on reading glasses and free access to antibiotics. This has effectively addressed the unjust and abrupt removal of such benefits by the previous administration.

On the other hand, the opposition will most probably intensify its criticism of the following issues:

- ? the electoral pledge relating to the free delivery medicines to patients' homes is still stuck in the pilot phase [which started in April 2016].
- ? the public-private partnership relating to Karen Grech Hospital, St Luke's Hospital and Gozo General Hospital between the Maltese government and Vitalis Global Healthcare has been envisaged to cost the government a whooping €55 million annually for medical services that are currently offered through the national health service.
- ? the agreement which was announced in 2015 between the Ministry of Health and the Queen Mary University of London, for the opening of a medical school in Gozo foresaw the opening of a campus of the Barts and the London School of Medicine and Dentistry. Initially, the government stated that the medical school would commence operations to all effects by September 2016. Last February, the government stated that the first students would be accepted in September 2017, whilst the new medical school building would only be ready in September 2018. Further to this, during these last months, medical students have consistently protested that such privatisation of medical education in Malta would dilute the medical school's clinical and education resources.
- ? although the 2017 budget announced that Type 2 diabetic patients will start benefiting from an *unspecified* amount of free glucose sticks, no indication of the commencement period of this service has been given.

Further to the above, the opposition will most probably also criticize the fact that the construction of the €100 million, 200-bed, private St John Paul II hospital at Smart City has not even commenced. During a press conference in March 2015, the government stated that the hospital was to open in 2017...

At this stage, only time will tell whether these predictions are correct…

Ian Ellul

Cover: Santo Spirito hospital pharmacy in Rabat. This is the oldest pharmacy in Malta dating back to the late 16th century.

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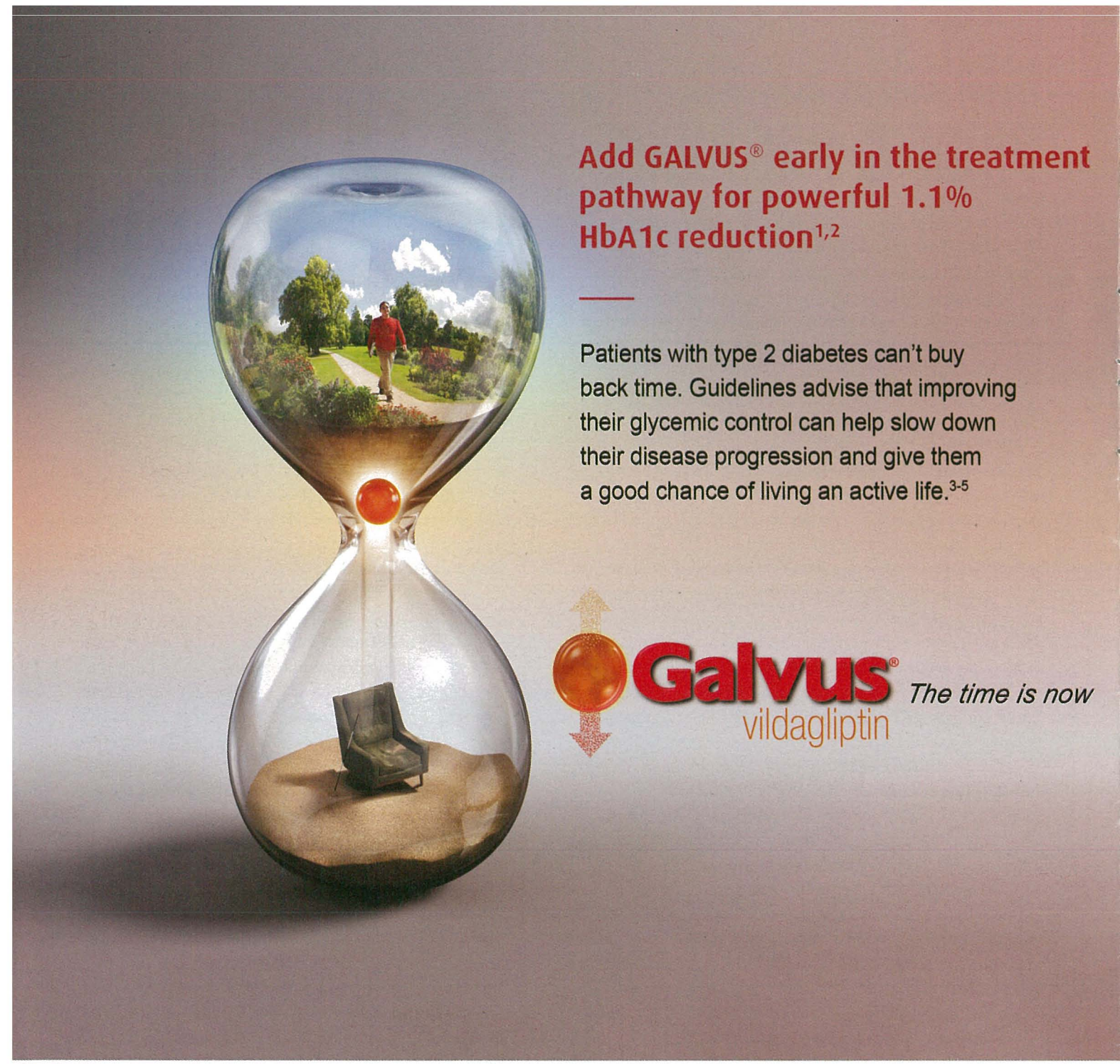

Add GALVUS® early in the treatment pathway for powerful 1.1% HbA1c reduction[1,2]

Patients with type 2 diabetes can't buy back time. Guidelines advise that improving their glycemic control can help slow down their disease progression and give them a good chance of living an active life.[3-5]

Galvus® vildagliptin

The time is now

Galvus®
PRESENTATION: Each tablet contains 50 mg of Vildagliptin. **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: i) As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. ii) 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. iii) 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 metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea 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 dual combination with a sulphonylurea, the recommended dose is 50mg once daily in the morning. 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. 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. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. Galvus is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy have not been established and no data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. No dose adjustments are necessary in elderly patients (≥ 65 years). **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 and Galvus should be used with caution in these patients. Galvus should be used with caution in patients with renal impairment. Galvus should not be used in patients with hepatic impairment. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class I-III treated with Vildagliptin is still limited. There is no experience with NYHA class IV and therefore use of Vildagliptin is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Exercise caution in patients with a history of acute pancreatitis. Patients with Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding, since no studies on the effect on human fertility have been conducted for Galvus. **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. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **ADVERSE REACTIONS:** Monotherapy: Common (>1/100 to <1/10): dizziness. Combination with metformin: Common: hypoglycaemia, tremor, headache, dizziness, nausea. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. For a full list of Adverse Reactions please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/003. **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 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2017-MT- GAL-09-MAR-2017

Eucreas®
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 adult 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 adult 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. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (GFR < 30 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. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. GFR should be assessed before treatment initiation and regularly thereafter. 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. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued at the time of surgery under general, spinal or epidural anaesthesia and resumed no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. The IV administration of iodinated contrast agents can lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. 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. A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3 6 months.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. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **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 due to an increased risk of lactic acidosis, iodinated contrast agents, 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 and products which can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop 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) angiodema, 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, Frimley Business Park, Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/021, EU/1/07/425/027. 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 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2018-MT-EUC-12-DEC-2016

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Galvus vildagliptin

Eucreas vildagliptin/metformin

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ISSUE GUIDE

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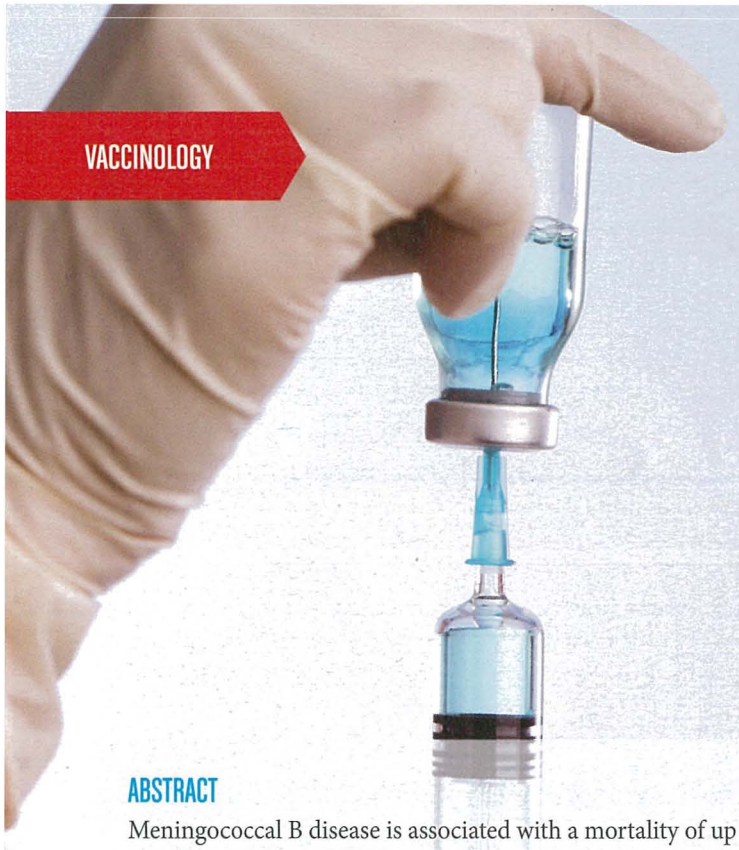

MENINGOCOCCAL B VACCINATION: A NOVEL APPROACH

SIMON ATTARD MONTALTO

ABSTRACT

Meningococcal B disease is associated with a mortality of up to 10% and significant morbidity in survivors. Attempts to produce an effective vaccine based on established methods over several decades, have succeeded in designing vaccines suitable only for local and strain-specific outbreaks. To date, the 4CMenB vaccine is the first preventative measure that is effective on a global endemic level and could potentially cover against 80% of isolates that cause this devastating disease. Although costly, this vaccine appears to be safe and can be given with other vaccines. Early trials of a 3+1 infant schedule have shown encouraging levels of seroprotection at 13 months of almost 100% for all four vaccine components. Results from widespread national programmes have shown uptake levels for the vaccine in excess of 95% of the target population, and significant reductions in invasive meningococcal B disease by more than 50% of cases within just 10 months of starting the programme. Long term surveillance for late adverse events and to determine the duration of protection is ongoing, and countries will need to independently establish the cost-benefit and feasibility of a 4CMenB programme.

Key words: Meningococcus B, Vaccination.

INTRODUCTION

Although relatively uncommon, invasive meningococcal disease (IMD) is one of the most deadly infections affecting healthy infants, children and young adults. Out of a total of 12 circulating capsular groups of *Neisseria meningitidis*, just 6 account for over 90% of significant infection[1]. In Europe, North America and Australasia, most of these cases are due to meningococcal capsular group B and, to a lesser extent, group C organisms, whereas group A is endemic in Africa (Figure 1)[2]. Silent nasopharyngeal carriage of *N. meningitidis* can be as high as 10% within the adult population during the 'cold and flu season', increasing the risk of transmission especially from persons in close contact in confined spaces. Although this accounts for the 'case clusters' during social events, amongst army recruits and university students[3], most cases are sporadic and the reason why some individuals appear to be more susceptible and go on to develop invasive disease is not clearly understood. Invasion occurs after a short incubation period of an average of 4 days (range 2-10 days) and, in the majority of cases, results in meningitis, septicaemia or both. The inherent severity of these conditions, combined with a fulminating course associated with an immunological cascade with serious complications including disseminated intravascular coagulation, shock and cardiovascular collapse, results in an overall case fatality rate of around 5-15%[4,5]. In those who survive, significant long term morbidity is present in around 10-20% and includes loss of digits and/or limbs, renal failure, blindness, deafness, cerebral palsy, cognitive impairment and epilepsy[5].

The rapidity of the infection and alarmingly high mortality and morbidity have ensured that meningococcal disease retains a high profile within medical circles as well as the general public. A significant amount of effort and resources have been directed to treat the acute illness, but also to prevent disease in the first place through vaccination. This has been very successful for some capsular groups including Men A[6] and C[7], but has been singularly difficult with regard to Men B disease where organism-derived antibody-inducing antigens within existing vaccines closely resemble human antigens and are, therefore, recognised as 'self' and render these vaccines non-immunogenic[8]. After decades of disappointment with early vaccines, a totally novel approach was required and this has now been successful in creating a vaccine that generates protection against 66-92% of circulating capsular group B *N. meningitidis* strains[9].

DISCUSSION

THE BURDEN OF DISEASE

In 2012, surveillance by the European Centre for Disease Prevention and Control (ECDC) confirmed that IMD comprised 43% meningitis, 29% septicaemia, 21% combined meningitis and septicaemia and the remaining 7% included septic arthritis, pneumonia, conjunctivitis, cervicitis, pericarditis and endocarditis[10]. This pattern of disease is true for both meningococcal B and C, although septicaemia is more common with group Y (50% versus 30% meningitis alone and 10% combined), whilst both meningitis and septicaemia comprise 40% of cases for group W and 45% for group A (versus 25% with meningitis and 15% septicaemia alone)[11].

IMD generally affects infants and, to a lesser extent, preschool-age children, adolescents and young adults. This is true both for epidemics and during natural background infection. For example, during the Men B epidemic in New Zealand over 1991-96, the incidence was 142/100,000 in infants and 73/100,000 for preschool children[12], whilst the non-epidemic infection rate for Men B in Europe over 2014-16 was 10.5/100,000 in infants, 2.5/100,000 for 1-4 year olds, 0.8/100,000 for 5-24 year olds and 0.2-0.3 in older age groups[13]. Gender does not appear to be a factor, with infection rates being similar for boys and girls.

A comprehensive epidemiological review of IMD in Malta[14] has confirmed an overall incidence rate for all types of meningococcal disease in 2000-2012 of 1.7/100,000, well above the European average of 1.1/100,000 for the same time period. The individual incidence rate was 0.99 and 0.3/100,000 for groups B and C, respectively, and the case fatality rate was above the European average, particularly with regard to Men C with 21% of cases compared with 11-15% for the rest of Europe[14]. Indeed, these figures would convincingly support the case for nationwide, population-based protection against Men C disease, particularly since several effective Men C vaccines have been widely available for almost two decades[15]. In contrast, this has not been the case for Men B where effective vaccine development has proven to be very difficult.

EARLY MEN B VACCINES

Early vaccines against Men C were purely polysaccharide-based and were designed to generate immunity against the meningococcal capsular polysaccharides. These vaccines were poorly immunogenic especially in those under the age of two, and had no effect on nasal carriage with waning protection over time[16].

Protein-polysaccharide conjugate vaccines were later developed. These were found to be safe and effective, even in infants, against Men A, C and in combination e.g. ACWY. Further development of these vaccines with, for example, alterations in the adjuvant or type of carrier protein used, improved the vaccines immunogenicity[17], and these conferred effective long term immunity. Consequently, over the past 15 years or so, many Men C/ACWY combination vaccines have been introduced into routine national schedules with very good effect. In the UK, nationwide Men C immunisation commenced in November 1999 and has reduced the rates of Men C disease in children to almost no cases per year[18].

The situation with Men B was different. Unlike other meningococcal capsular groups, the Men B organism contains polysialic acid within its outer capsule, a compound that also forms part of the neural cell adhesion molecule (NCAM) in humans. This homophilic binding glycoprotein is expressed on several human cells including neurones, glia and skeletal muscle. Hence, its introduction within classical protein-polysaccharide conjugate vaccines derived from meningococcal B capsular components ensures that the vaccine is recognised as a 'self-antigen' and immune-tolerance guarantees a poor antibody response. An alternative approach was to revert to 'whole cell' vaccines but Men B strains are widely diverse and, therefore, several whole cell vaccines would be required to cover all major Men B pathogens. Other vaccines utilising protein antigenic components from the outer membrane vesicles (OMV) that are shed by the meningococcus during replication were developed. However, since the OMVs are strain-specific, these vaccines are only effective against meningococcal strains sharing the same proteins found in the OMVs.

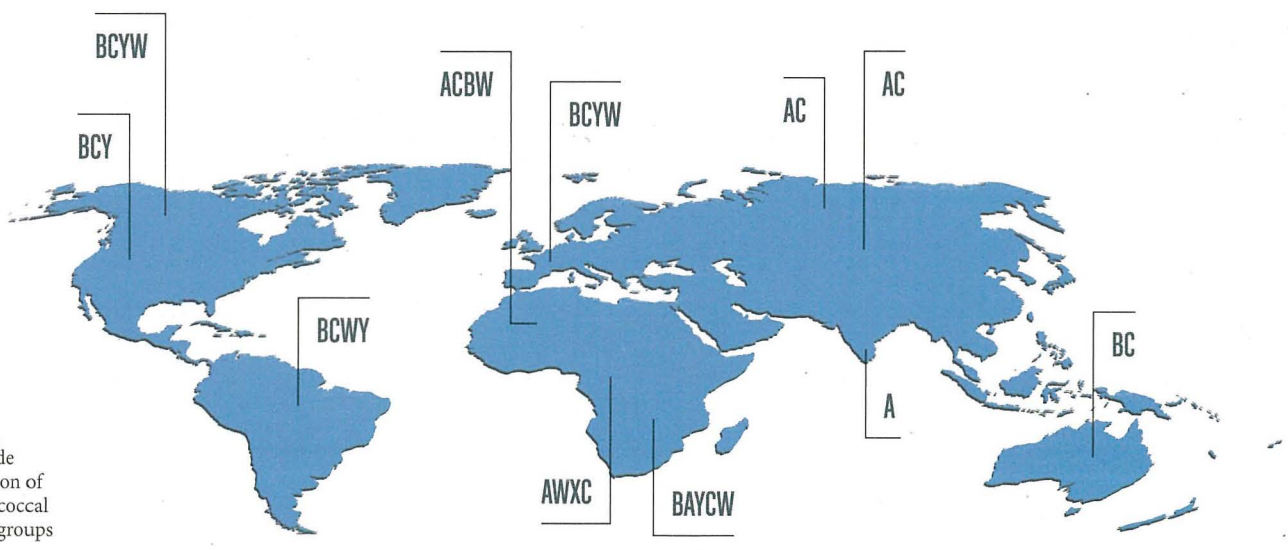

Figure 1. Worldwide distribution of meningococcal capsular groups

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In practice, they proved effective in isolated outbreaks involving single strains in Norway in 1990 with 57.2% protection[19], Cuba in 1990 with 83% efficacy[20], and Normandy, France in 2003[21]. In effect, these were tailor-made vaccines for isolated outbreaks and an alternative approach was required in order to design a vaccine that would offer effective protection for global endemic disease.

A NEW APPROACH TO VACCINATION

Reverse vaccinology was the phrase coined to describe this new approach. Using modern gene sequencing techniques, the entire meningococcus genome was determined, and repeatedly put through computer programmes to identify gene sequences that coded for antigenic proteins that, in turn, resulted in an immune response. To be 'eligible' for possible inclusion into a vaccine, these genes also had to be common to different meningococcal strains. Thousands of candidate genes were whittled down to just three major antigenic proteins (Table 1), and these were then combined with the OMV protein antigen from the strain-specific OMV vaccine developed in New Zealand in 1997, to create a new Men B vaccine[22].

Table 1. Components of 4CMenB vaccine

Component	Action
NadA	Promotes adherence to human epithelial cells
NHBA	Binds heparin, prolonging bacterial survival in blood
fHbp	Binds factor H, allowing bacterial survival in blood
NZ PoA 1.4	Induces strain specific bactericidal response

TO-DATE THERE HAVE BEEN NO MAJOR SAFETY ISSUES, WITH AROUND 25% OF VACCINEES DEVELOPING A FEVER. THIS DOUBLES TO 50% IF 4CMENB IS GIVEN IN COMBINATION WITH OTHER VACCINES

EARLY RESULTS OF NEW VACCINE

The resulting four-component Men B (4CMenB) vaccine was, during subsequent clinical trials, found to be safe and highly immunogenic against several strains of Men B[23]. A three dose priming course in the first few months (2, 4 and 6 months) followed by a booster dose at twelve months was shown to produce very high and persistent bactericidal antibody levels against all four components at 13 months[24]. This vaccine is based entirely on subcapsular meningococcal components and can, therefore, potentially offer some cross protection against other meningococcal serotypes that share these core proteins. Variations within Men B strains will account for some differences in immune response after vaccination, but a comprehensive review of Men B strains by country have predicted adequate cover against 80% of all currently circulating isolates (ranging from 66% in Canada to 91% in the USA, Figure 2)[9].

To-date there have been no major safety issues, with around 25% of vaccinees developing a fever. This doubles to 50% if 4CMenB is given in combination with other vaccines and, for this reason, it has been recommended to co-administer paracetamol prophylactically together with the vaccine. This reduces the risk of fever to 'background' levels whilst also alleviating pain, fussiness and other minor adverse events[25]. Concerns have been raised that co-administering paracetamol reduces the immunogenicity of 4CMenB vaccines. However, although antibody responses to the 4CMenB vaccines are reduced with paracetamol, titres are still maintained well above seroprotective levels[26].

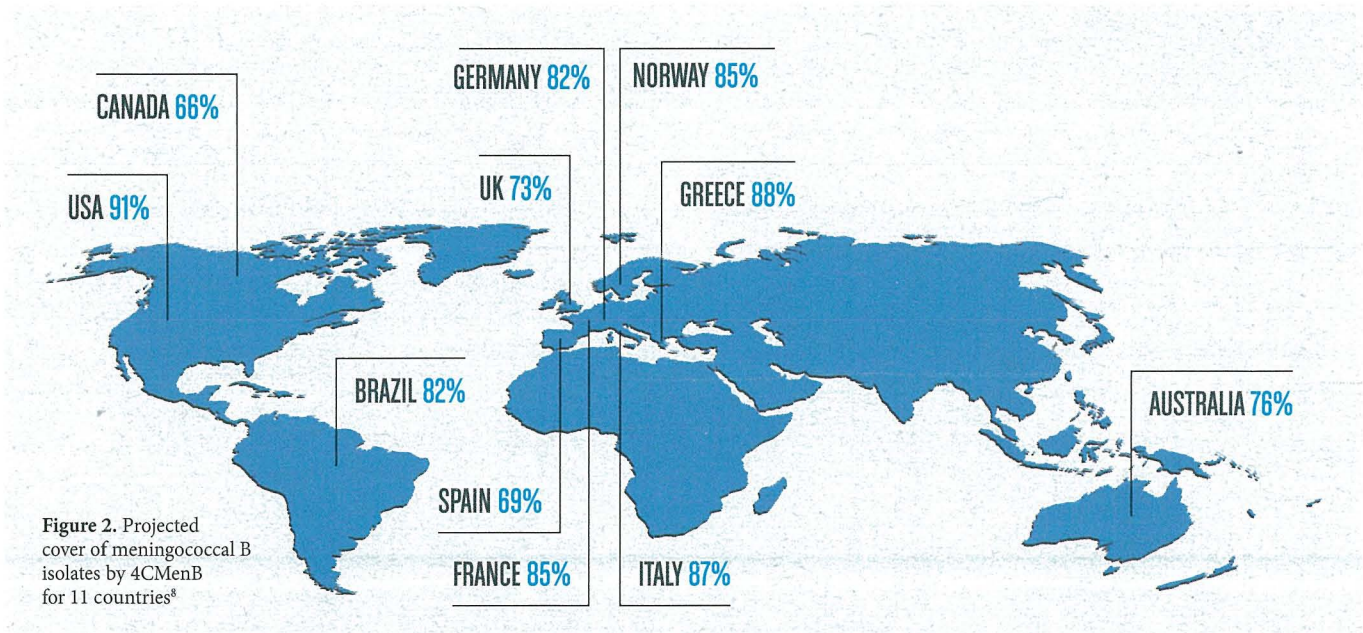

Figure 2. Projected cover of meningococcal B isolates by 4CMenB for 11 countries[8]

FUTURE CONSIDERATIONS FOR 4CMENB

The difficulty, duration and complexity of developing this new vaccine have resulted in a hefty price tag (estimated at **approximately €100 per dose**, for a 3 or 4-dose programme). Given that meningococcal B is a rare disease affecting roughly 1:100,000 and has a varying incidence with fluctuating peaks and troughs over several-year cycles, the price for national vaccine coverage may be difficult to justify. Furthermore, there may be problems introducing yet another multi-dose vaccine into busy national immunisation schedules. On the other hand, this is offset by the severity of this disease with 10% mortality and 20% significant morbidity, and effectiveness of the vaccine. Indeed, the introduction of 4CMenB in Quebec, a highly endemic Men B region in Canada in 2013, and to selected university students in the US, resulted in no MenB cases and no safety issues in vaccinees[27]. Every country will need to weigh all options on an individual basis and, for example, the UK have altered their position from "not cost effective" in 2013 to **"recommended for national coverage" by 2014 and introduced in 2015**. Uptake for the first and second doses in the UK have now reached >95% and >90% of the target population, respectively, and within 10 months of introducing 4CMenB, the number of cases with Men B meningitis and/or septicaemia have halved.

Other countries like France have introduced 4cMenB at a local level with encouraging preliminary results[28].

Clearly, the results of post-immunisation surveillance from all these programmes will be awaited with great interest. Once wide coverage is attained and herd immunity established, it may well be possible to reduce the number of priming and booster doses required, as happened with Men C and Men ACWY vaccine programmes[29].

CONCLUSION

To-date, the 4CMenB vaccine is the first effective preventative measure against this devastating disease. Although costly, it appears to be safe, and can be given with other vaccines although co-administered paracetamol is recommended. Long term surveillance to exclude any late adverse events and to determine the effectiveness and duration of protection is required. Individual countries will need to complete an individual country-specific exercise to establish the cost-benefit and feasibility of a 4CMenB programme.

Acknowledgement

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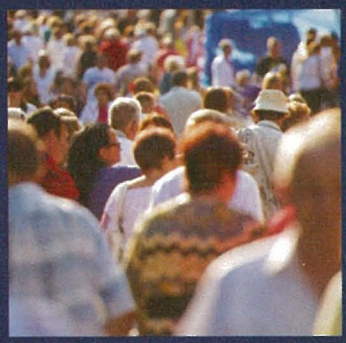
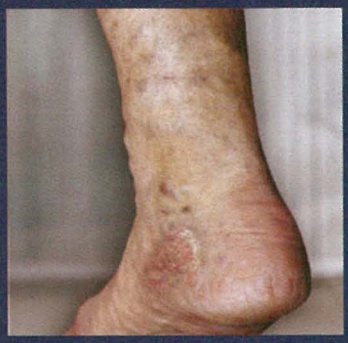
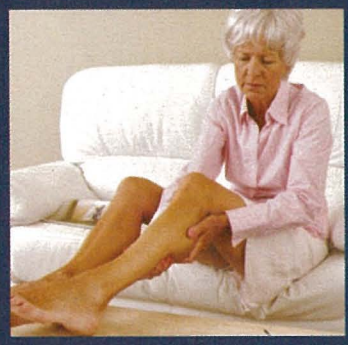

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1.Nicolaides A et al. *International Angiology.* 2014;33(2):126-139.
2.Pascarella L et al. Phlebolymphology. 2016;23(1):20-30.
3.Takase S et al. Eur J Vasc Endovasc Surg. 2004;28:484-493

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DRIVE & USE MACHINES. No studies have been performed. However, on the basis of the overall safety profile, it has no or negligible influence on these abilities. **UNDESIRABLE EFFECTS** *Common:* diarrhoea, dyspepsia, nausea, vomiting. *Rare:* dizziness, headache, malaise, rash, pruritus, urticaria. *Uncommon:* colitis. *Frequency not known:* abdominal pain, isolated face, lip, eyelid oedema. Exceptionally Quincke's oedema. **OVERDOSE PROPERTIES**: No case of overdose has been reported. **PHAMACDYNAMIC PROPERTIES**:V ascular protector and venotonic. Daflon 500 mg acts on the return vascular system: it reduces venous distensibility and venous stasis; in the microcirculation, it normalizes capillary permeability and reinforces capillary resistance. **PRESENTATION**: Pack of 30 film-coated tablets of Daflon 500 mg.
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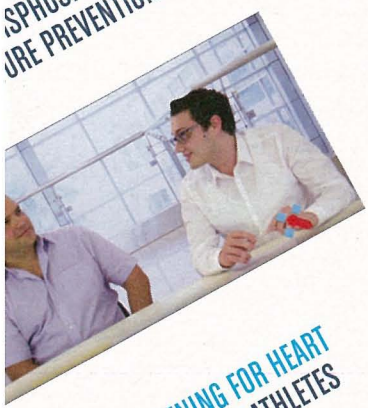

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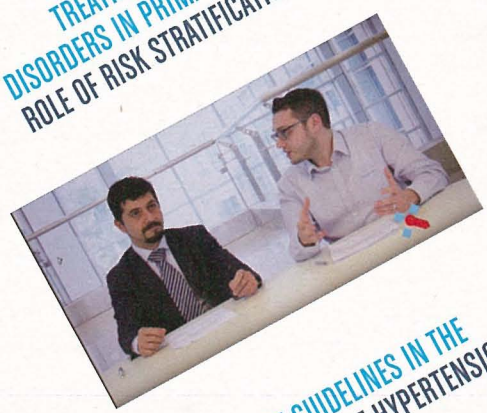

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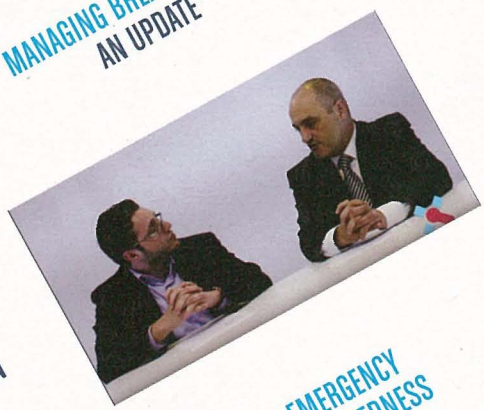

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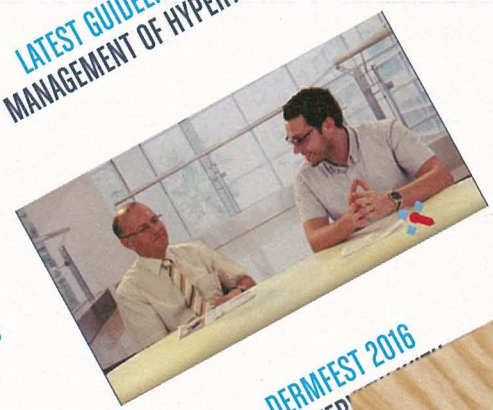

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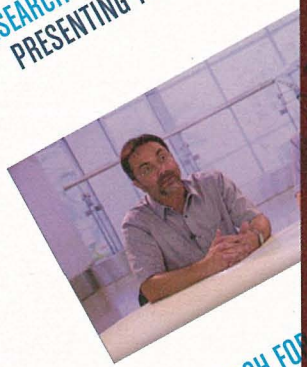

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DOES THIS SARCOMA NEED DRASTIC SURGERY?

Short accounts of interesting cases, some medical disasters, involving pathology and clinical practice, from the recollection of *Prof. Albert Cilia-Vincenti.*

I started my postgraduate histopathology training, in 1971, at The Royal Marsden Hospital in Fulham Road, Chelsea, situated opposite The Brompton Chest Hospital. These are old hospitals with a reputation. The first open thoracic operation in the world was said to have been performed at the Brompton to remove a lung tumour which turned out, on pathological examination, to be a solitary secondary deposit from a renal cell carcinoma, and with claimed long patient survival after the pneumonectomy and excision of the kidney bearing the primary tumour.

The Royal Marsden was previously called The Royal Cancer Hospital – the name was obviously changed not to add more anxiety to already very worried patients. Its consultant surgeons were trail-blazers in oncological surgery – often very drastic operations few surgeons could perform. Extensive surgery to remove the primary tumour and all the local lymphatic field was then believed to be the only way to cure cancer. Mind you, the oncological surgical skill to perform an adequate first local clearance of the primary tumour is still crucial for possible cure, depending on the tumour type, such as, low grade soft tissue sarcomas, where cure is only possible if the first excision is complete and no local recurrence occurs.

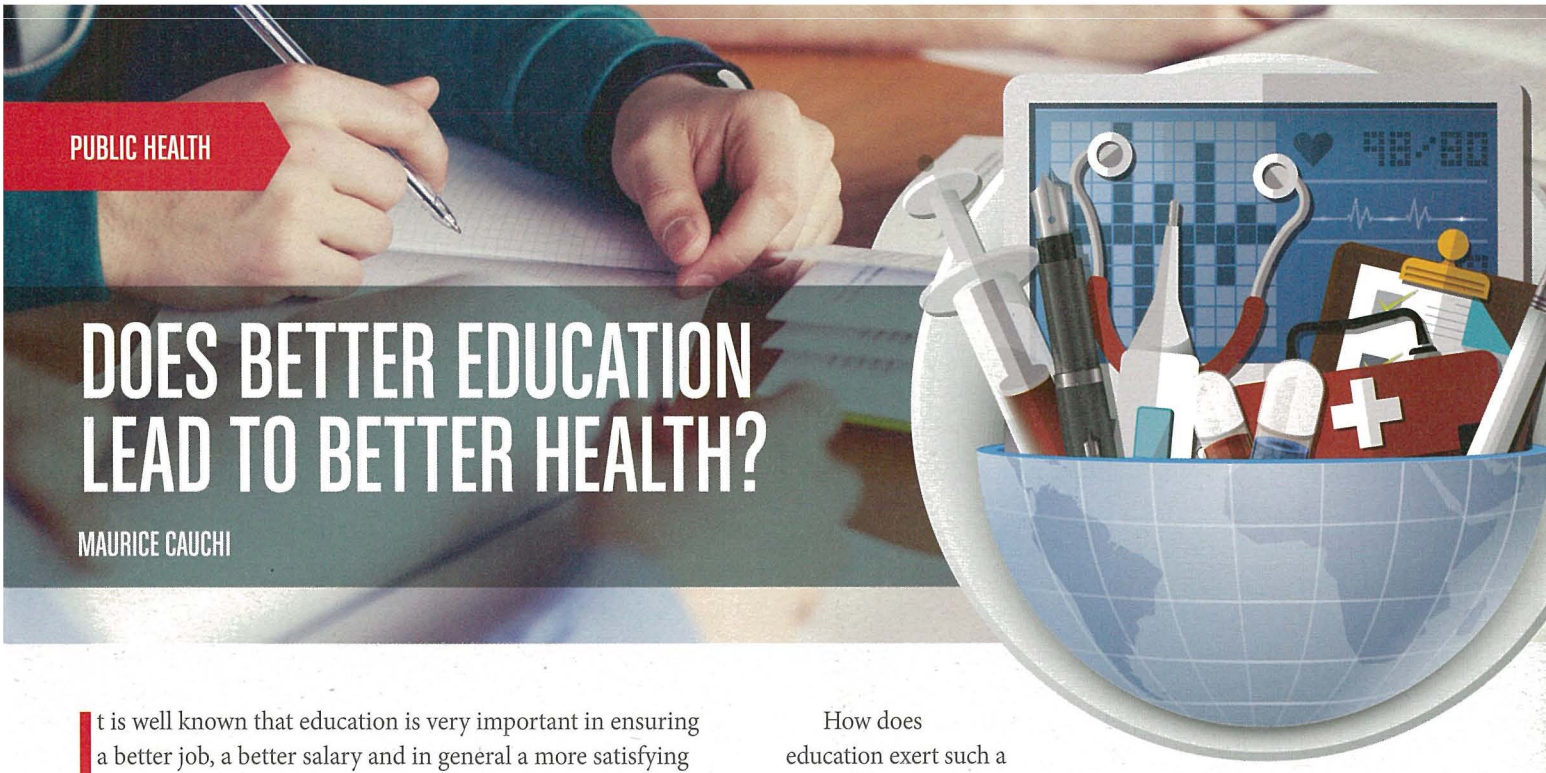
Better understanding of tumour biology and the different tumour propensities for metastasis, eventually led to less drastic surgery. When I got to the Marsden, Mr Raven, the senior surgeon, had just retired. He had published a series of surgical oncology books, and his treatment for breast cancer, for example, was often the Halsted radical mastectomy, an attempt to remove internal thoracic intercostal nodes, a bilateral oophorectomy and adrenalectomy. Soon after, Veronelli and Bonadonna in Milan, showed that lumpectomy and their introduction of adjuvant chemotherapy gave better survival than all that drastic, disfiguring surgery.

The Marsden's histopathology department was also highly regarded, particularly because of its head, Professor Noel Gowing. He was recognised as a leading diagnostic surgical pathologist, not only in UK, but also in America. A visiting American oncologist, taking part in a clinico-pathological conference at the Marsden in 1972, pointed out that the Marsden's osteosarcoma survival figures were poorer than American ones, and that the reason was that Gowing's diagnoses were accurate while some American cases had been benign lesions over-diagnosed as osteosarcoma. One warning drummed into us at the Marsden was that the most serious mistake in oncology was a wrong diagnosis of cancer in the relatively young, leading to unnecessary, possibly mutilating surgery and/or radiotherapy and chemotherapy. This warning would haunt me throughout my career.

Gowing used to receive a lot of material for second opinion. Sometimes the referred histological slides would accompany the patient. One such case I remember was a teenage girl from northern England, sent to the Marsden for surgery to remove an "osteosarcoma of the breast". The girl had reportedly fallen off a horse, hitting her chest against the ground and, soon after, a firm, deep, enlarging breast lump was noted. Gowing showed us the plain X-rays of this mass situated between the breast and the chest wall and characterised by fine ossifications. He asked us to note that the ossifications, interpreted as evidence of osteosarcoma at St Elsewhere, were forming a sort of ring at the periphery of the mass and that there were none in its central tumour zone. Turning to the histological slides, he explained that the centre of the mass consisted of undifferentiated, proliferating connective tissue which, as it grew outwards, was maturing and differentiating towards bone formation, responsible for the X-ray features. This was not osteosarcoma – this was a focus of "myositis ossificans" following muscle injury. All that was needed was minimal surgery to remove the lump. Sometimes the Marsden was a purveyor of happiness – good, rather than bad, news.

This is now the mid-1980s and I'm a consultant histopathologist in Winchester. A local teenaged girl has had a deep thigh lump biopsied. It is radiologically attached to the femoral periosteum and suspicious of osteosarcoma. The lump apparently followed soon after a fall from a horse and grew rapidly. I ask for the X-rays because I suspect this sounds similar to the case I remember at the Marsden. Indeed it was, both radiologically and histologically. Great relief all round – and the pathology department gains credit with its audience – the local medical community. But don't be overconfident Mr Pathologist and watch out for banana skins which might be round the corner.

ONE WARNING DRUMMED INTO US AT THE MARSDEN WAS THAT THE MOST SERIOUS MISTAKE WAS A WRONG DIAGNOSIS OF CANCER IN THE RELATIVELY YOUNG, LEADING TO UNNECESSARY DRASTIC SURGERY AND/OR RADIOTHERAPY AND CHEMOTHERAPY. THIS WARNING WOULD HAUNT ME THROUGHOUT MY CAREER



DOES BETTER EDUCATION LEAD TO BETTER HEALTH?

MAURICE CAUCHI

It is well known that education is very important in ensuring a better job, a better salary and in general a more satisfying social life. Perhaps less well appreciated is the effect that education has on the health of the individual.

The level of education is definitely correlated with life expectancy. A report by the Robert Wood Foundation in the US (2013)[1] shows that life expectancy is higher in college graduates compared to those who did not finish high school (79.7 versus 72.9 years respectively for males, and 83.5 versus 78.4 years in females). In Europe a higher education seems to add an extra three years to life expectancy[2].

Differences in life expectancy have been attributed to various factors. In the US, one of the most 'unequal' countries on earth, these differences have been seen as indicating racial differences. However, they are much more significantly correlated with the level of education. Michael Marmot in his book *The Health Gap*[3] emphasizes that "So-called racial differences in health are related to degrees of social disadvantage and discrimination."

In Europe, there is quite a significant difference in life expectancy between the various countries. At age 25, a time when peri-natal mortality rates are no longer relevant, citizens of most countries in the EU can expect to live another 60 years.

Perhaps more significantly, within any one country, the difference in life expectancy between those with a minimal or no education compared to those with a higher education can vary by 20 years or more[4]. These differences are particularly marked in eastern European countries (including Estonia, Hungary, Romania, Poland, Czech Republic and Croatia), where the difference between life expectancy of the poorly educated can be 20-30 years less than those with a tertiary education. Western European countries, including Malta, have much smaller differences between the two groups. To note also that women in general not only seem to have a longer life expectancy, but also that the difference between those with lower education and those with a higher education is not so marked.

Moreover, as the Robert Wood Foundation report remarks, there is a definite probability of propagating parental characteristics to the future generation. The level of education reached by children had a direct correlation with that of their parents.

How does education exert such a powerful effect on life expectancy?

A number of health conditions, which may be responsible for reducing life expectancy, seem to correlate with level of education. For instance, the Robert Wood Foundation report shows that:

- Those with a college education had a reduced risk for diabetes, heart disease and being overweight;
- A higher level of education seems to reduce the incidence of smoking. Those with a higher education (16 years of education or more) seem less likely to smoke compared to those with those with a lower level of education (11 years or less). In most western countries, the proportion of those who smoke is much higher in those with a lower education level compared to those with a higher education. In the US, for instance, those with a lower education level are two-and-a-half times more likely to be smokers compared to those with a higher education: a ratio of 2.5. In other countries this ratio varies from 2.3 in Canada, 1.35 in Netherlands, 1.60 in England and 1.14 in Italy. Curiously, in a couple of European countries, those with a higher education tend to smoke more than those with a lower education, with ratios for France being 0.60, and for Spain 0.90[2]. The above figures apply to the male population. While in general, the proportion of women smokers in the community is less than in males, the effect of education on smoking is the same in women as in males. (To note that in some countries, like Spain, Italy, France and Japan, women with a higher education smoke more than those with a lower education. There is no clear reason for these intriguing differences).
- There seems also to be a direct correlation between lack of education and the tendency to develop obesity. In several countries in Europe, both males and females who are better educated tend to be less obese[2]. So there seems no doubt that education has a very beneficial effect in preventing obesity, with all its accompanying health issues.
- The mortality rate in infants of mothers who did not have a college education was approximately double that for those with a college education (8.1 per 1,000 live births compared

to 4.2/1000 respectively). If this difference is significant for developed countries it is far more significant for developing countries where infant mortality rates for those with no education can reach over 100 per 1000 live births[5]. In particular, as Marmot emphasizes "The mother's education is a much stronger predictor of infant mortality than is household income or wealth"[3].

- Fertility rate seems to be affected by the degree of education: women with more education have fewer children. In Nigeria, for instance, the average number of births varies from 6.1 in those women with no education to 4.2 in those with a secondary or higher education[3].
- Education is empowerment: a situation unheard of in a western society is the degradation that absence of an education can lead to. Women in sub-Sahara regions were asked if it was acceptable for husbands to beat their wife if they refused to have sex with him! Nearly half of uneducated women in Ethiopia agreed that this is acceptable, compared to only 11% with a secondary or higher education. Marmon interprets this as meaning that education makes women less vulnerable, which presumably would tend to reduce domestic violence[3]. He concludes that: "... a focus on educating girls is the best single contributor to empowerment of women, with improvements in national and community development and health for women and their children."

The government of Malta is well aware of the impact that education has on health and the relevance of these two considerations on the Maltese society. The 2014 budget shows that Malta spends 6.0% of its income on health and 5.8% on education (compared to the EU average of 7.2% and 4.9% respectively)[6].

The number of Maltese persons enrolled at the university has been steadily increasing over the last couple of decades, from around 6,000 in 1995 to over 14,000 in 2013[7]. This means that the proportion of 30-34 year olds holding a higher qualification rose from 9.3% in 2002 to 26% in 2013. Conversely, the proportion of 18-24 year olds who left school early (lower secondary education) has dropped from 53% in 2002 to 21% in 2013. However, this still does not compare favourably with the EU average where there was a higher proportion of 30-34 year olds who had a higher qualification in 2003 (37%), and a lower proportion of early school leavers (12%). In view of the importance of female education, it is gratifying to see that in Malta, in 2013, female participation in higher education was higher than that of men (29.5% compared to 22.6% in 30-34 year olds, respectively)[8]. Indeed, in 2013, the proportion of early school leavers was less in females compared to males (18% compared to 23%)[7].

So there can be no doubt about the effect of education on health and related social issues. While such deprivation is more obvious in developing countries, it also affects a considerable proportion of the population in so-called developed countries, particularly where inequality is rampant and enormous differences exist between rich and poor. As mentioned in the previous instalment[9], such pockets of inequality can be seen also in Malta.

Social deprivation, poverty and exclusion often lead to a poor education which in turn leads to health issues. "[T]he more education you have the better your health."[3]

The manifestations of inequality maybe more nuanced than used to be the case in the past: a simple formula which takes into account only family income may not give a whole picture of the degree of need. Deprivation in a western country does not simply refer to hunger or homelessness. It also involves inability to have resources that are considered standard within a community. These include: ability to pay rents, having a telephone and a colour TV like everybody else, have a meat or fish dinner two or three times a week, as well as other amenities including a family car, a washing machine etc. In Europe, it has been shown that deprivation of these items is associated with a worse health status[3].

A 'health development index' (HDI) developed by the UN, based on measures such as national income, education and life expectancy found that education and health have a big impact on HDI while income does not[3].

How does all this affect busy medical practitioners who are not expected to be social workers and who have rarely been educated in social issues as they affect health?

What the above information seems to suggest is that in our efforts to diagnose the root cause of disease we would do well to assess also the level of education of our patients. Perhaps in our history-taking, in addition to the standard list of items known to impact on health, like 'weight', 'age', etc, we should add 'education level', seeing that it is such a determining factor in normalising health issues.

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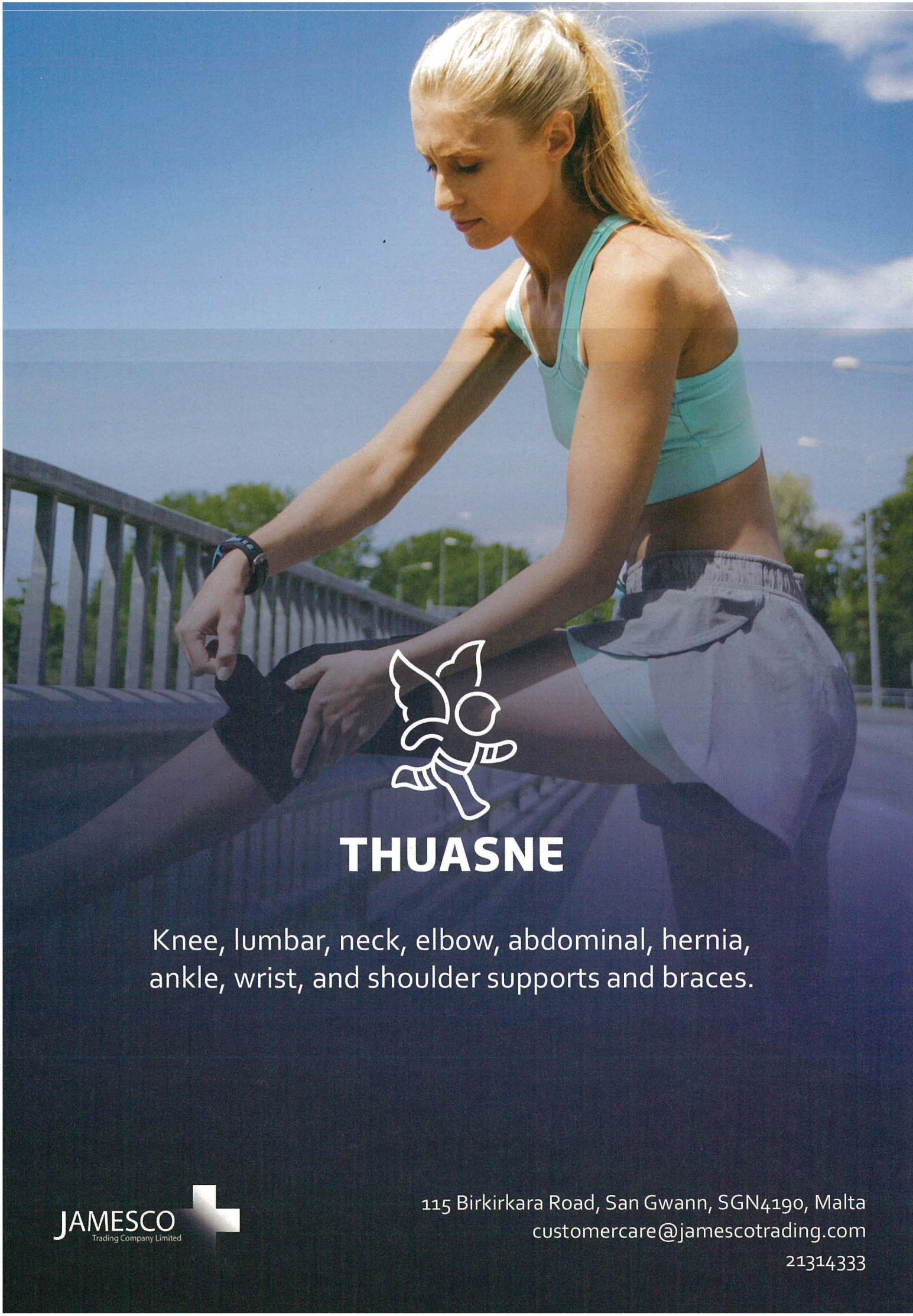
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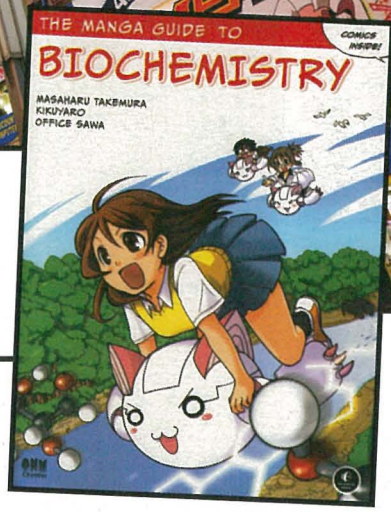
THE MANGA GUIDE TO BIOCHEMISTRY



Author: Masaharu Takemura
Illustrator: Kikuyaro
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Paperback: 272 pages
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Print ISBN-13: 978-1-59327-276-0

MICHELLE MUSCAT

"The Manga Guide to Biochemistry" offers a unique take on more complex biochemical processes, presenting these in diagrammatic and intuitive forms, that would especially appeal to audiences who enjoy manga, as well as those who would potentially consider taking up a career in biochemistry, or related subject. It also provides a unique take on biochemistry for undergraduate students reading for a degree in the subject area, who may choose to leisurely read this to complement their more traditional textbooks.

As a manga enthusiast, the author was quite intrigued when a manga was first released on the market in 2009, and translated to English in 2011, that brought together both the more traditional manga artwork as well as simplified concepts of this subject discipline, albeit it is less focused on the clinical aspect of biochemistry. "The Manga Guide to Biochemistry"[1] offers a new and more refreshing perspective to other traditional textbooks, which could serve as a simpler, more engaging introduction to the subject matter for certain targeted audiences[2-6]. Although the book opens with some concepts of high school biology and chemistry, it overall mainly details the fundamentals of biochemistry such as discussions on carbohydrates; protein synthesis; glycolysis; the tricarboxylic acid cycle; primary, secondary, tertiary and quaternary protein structures; enzyme inhibition as well as basic information on nucleic acids. Additionally, the book also delves into specific subjects which are even more relevant to the clinical biochemistry counterpart such as centrifugation, electrophoresis and chromatography amongst others. It goes as far as discussing the Michaelis-Menten equation and calculating V_{max} and K_m, which to the author's knowledge, is an unprecedented move in the manga field. Interestingly, structures of Vitamin D3 as well as progesterone and testosterone are also illustrated. Mention is also made of the metabolic syndrome in the introductory section. This manga is in fact written by a PhD graduate who comes from a nutritional science background, and was proofread by professors in the field.

The book recounts the story of a girl named Kumi and her friend Nemoto who is studying biochemistry at university. Kumi is introduced to a beautiful associate professor in biochemistry, Choko Kurosaka. Kumi is seen to soar through the journey of intellectual growth and discovery, looking with wonder at charts which illustrate chylomicrons, low density lipoprotein and high density lipoprotein; exploring the pathophysiological mechanism of atherosclerosis and, at the end of it all, being her cheerful self and adding mayonnaise to her pancakes! The role of leptin is also introduced to Kumi, which is of particular interest to her since it is shown that she really loves food but is concerned about gaining weight. Detailed discussions of amino acid structures are given enthusiastically by Kurosaka , with Kumi appearing initially quite stunned at that point. Different types of enzymes - oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases - are illustrated on a board, and their functionality is explained to Kumi in a very intuitive, personified and diagrammatic way. The manga guide covers many other topics as well, and would be perfect for students who like manga and are interested in maybe taking up a career in biochemistry.

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Assignment in Northern Ireland, 1972 – 'Captain Benċini reporting for duty, Sir'

A DOCTOR'S LIFE IN THE ARMY

For this issue, MARIKA AZZOPARDI meets up with COLONEL CHEVALIER DR RAYMOND BENĊINI to talk about his long and rewarding career in the British Army. The first time she met him was in 2002 when she reviewed his book "Hitler's Deputy was One of my Patients - A Maltese Doctor in the British Army." This time round, Dr Benċini speaks candidly about his personal experiences as a military doctor.

TS: HOW LONG HAVE YOU BEEN ASSOCIATED WITH THE BRITISH ARMY AND HOW DID THIS ASSOCIATION COME ABOUT?

I served as a uniformed medical officer for 27 years, of which I spent over 20 years acting as a GP Trainer. However, my association as a doctor in the army so far spans 46 years. Even though I retired on pension as a full Colonel in 1998, I am still active and have since travelled as far as Brunei to perform GP locums. As a young man, I was interested in taking up languages at university. My father had other plans for me. He had been unable to complete his medical course at university due to the onset of WWII in 1939. Being the male son in line, I was expected to step in his shoes. I do not for one moment regret it. After completing my university studies and working at St Luke's Hospital for four years, I applied to join the British Army as a GP. Consequently, I became a Captain in the Royal Army Medical Corps in 1971.

Dr Benċini [left] with an American dentist in an Anglo-American rapid deployment exercise in the Mojave desert, California, mid-eighties

TS: WHERE WERE YOU BASED OVER THE YEARS?

In so many countries ranging from Germany to Hong Kong and many places in between. Consequently this did allow me to practise languages which I so enjoyed. I had a baptism of fire with one of my first postings. While serving in Germany, I was sent to Belfast in Northern Ireland in 1972, just after the Bloody Sunday Massacre. I was doctor for the 1st Regiment Royal Horse Artillery, an elite regiment. My unit was based at Long Kesh Detention Centre, later known as The Maze, a barracks which housed mainly IRA and a few Loyalist internees. My worst experience was suturing an internee's calf wound, after a prison riot. He had to be held down by strong military policemen. Listening to continual screaming and verbal abuse was not the ideal scenario to perform a good suturing job. I was posted to Cyprus after my

Off to a mess night at Bergen-Belsen Hohne

Sporting an Italian Bersaglieri headwear, lent by Italian friends

time in Germany and Northern Ireland. A holiday posting one might have thought! How wrong could one be! The coup d'etat and Turkish invasion happened just one month after I set foot on the island. Other countries I worked in while serving in the RAMC were UK, Belgium, Hong Kong USA and Italy ... I also worked at the British Military Hospital in Berlin from 1976-1979.

TS: WAS THAT WHERE YOU MET RUDOLPH HESS?

Yes indeed. One fine day, I was called by my Commanding Officer. Would I be happy to look after Hitler's Deputy at the Allied Prison in Spandau? I was already a Major then and I thought it would be a pretty interesting experience. This was how I acquainted myself with a man who was very well mannered and who, upon discovering I was Maltese, became very friendly towards me.

TS: WHAT WAS YOUR MOST EXOTIC STATION?

Definitely Hong Kong where I spent three years. During that period my family and I had the opportunity of travelling all over Asia. I spent one year in a British Military Hospital there and two years as the Commanding Officer of the New Territories Group Practice in Sek Kong. I was assigned to take care of the British soldiers, the Nepalese soldiers in the British Army known as the famous Gurkhas, and Chinese personnel.

At work as Lieutenant colonel, mid-eighties

TS: CAN YOU IDENTIFY YOUR UNIQUE EXPERIENCES AS A DOCTOR IN THE FAR EAST?

Examining Chinese civilians who worked in our barracks in the New Territories in Hong Kong. Since they spoke Cantonese, I always required the intervention of a translator who was generally my secretary. I was always impressed by the lack of emotional expression of the Chinese - for them emotional reactions were considered a weakness. I also saw a number of cases of Tuberculosis among them. Contact tracing was a nightmare!

As commanding officer, Dr.Bencini (middle front row) sits with his training wing's staff, and the last regimental medical assistants course participants - NTGP Hong Kong

TS: WHAT IMPRESSED YOU MOST OF THE FAMILIES OF SOLDIERS?

Since I not only looked after the health of the soldiers but also of their families, my main interest was family medicine. I found that a large percentage of family members suffered a considerable number of health issues mostly due to separation anxiety. This happened when the fathers or mothers were on exercises or stationed in war zones. A case in point was the Gulf War in 1991. I was the senior doctor in Munster, Germany at the time, with a team of some seven doctors under my supervision. All my doctors were sent to Iraq, apart from myself since I was senior doctor. They were replaced by Reservist doctors, i.e doctors who had previously served in the RAMC. There was a great deal of concern about chemical weapons, which we now know was unfounded. This caused extreme worry to family members. At the time, the West was convinced Saddam Hussein had anthrax as a weapon, and so our soldiers were vaccinated against anthrax. Sadly many of them had nasty reactions to the vaccines.

Dr Benčini with his family in a visit to Tai O, the sea village on stilts in Lantau, Hong Kong

TS: HOW HAS THE BRITISH ARMY CHANGED OVER THE YEARS?

Considerably! During my 27 years serving in the British Army, the vast majority of serving soldiers were proper professionals - they signed a 22-year contract to serve. Now to start with, the number of such soldiers has been dramatically reduced. Furthermore, the British Army now relies very much on part-time soldiers and former soldiers or reservists, just like myself. Finally, from a medical perspective I now see substantial difference in discipline and less submission to authority than previously.

ULTRASOUND OF THE INGUINAL CANAL PART I

PIERRE VASSALLO

Ultrasound has a major role in detecting disease in the inguinal region. A good knowledge of the anatomy and pathologic findings on ultrasound is required to reach a correct diagnosis.

The structure and function of the inguinal canal can only be appreciated when one understands what occurs at this site during the embryonic and fetal periods. The formation of the inguinal canal starts at the 7th week of gestation. In males, it represents the passage through which the testis passes from its intraabdominal location of origin to the scrotum, its normal location at birth. In females, it contains the round ligament of the uterus.

At around 7 weeks of gestation, the gonads (testes and ovaries) develop along with the kidneys from the urogenital ridges. The urogenital ridges are located on either side of the structures that will form the lumbar spine. The more medially located portion of the urogenital ridge forms the gonad and the lateral portion forms the kidney (Fig 1). A ligament called the gubernaculum is attached to the inferior pole of the gonad and extends inferiorly through the abdominal wall into the inguinal region to attach to the labroscrotal fold; the labroscrotal fold forms the scrotum in males and the labia major in females. In female fetuses, the gubernaculum is attached to the uterus in its mid-section. In male fetuses, the gubernaculum shortens and pulls the testis down from its original position near the spine into the scrotum (Fig 2). Due to the attachment of the gubernaculum to the uterus in female fetuses, the migration of the ovary halts near the uterus and the distal gubernaculum forms the round ligament.

All layers of the abdominal wall extend along the gubernaculum, testis and round ligament; they form the scrotal sac in the male (Fig 2). The passage through the different abdominal wall layers represents the inguinal canal, which contains the spermatic cord in the male and the round ligament in the female. An invagination of peritoneum that follows the testis into the scrotum, detaches from the main peritoneal cavity and forms the tunica vaginalis. This peritoneal invagination closes in the female. A persistent peritoneal communication in the

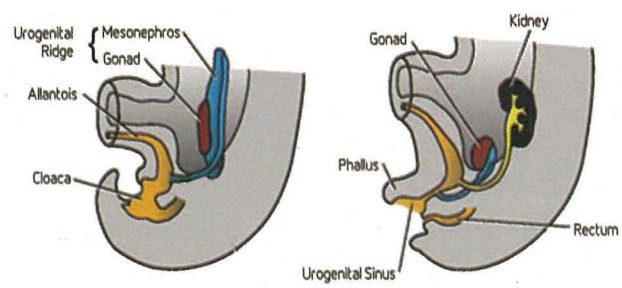

Figure 1. The kidney and gonad develop from a common structure, the urogenital ridge, that is located next to the structures that will form the lower spine in the embryo. The inner part of the urogenital ridge forms the gonad that descends into the pelvic/scrotal area, while the lateral part forms the kidney that retains its paraspinal location.

male is called a patent processus vaginalis (Fig 3), while in the female, it is called the canal of Nuck. A persistent processus vaginalis predisposes to an indirect inguinal hernia and a communicating hydrocoele.

The inguinal canal is circa 4cm long and extends above the inguinal ligament through the layers of the abdominal wall muscles, starting internally at the internal inguinal ring that lies just lateral to the origin of the inferior epigastric vessels and ending externally above and medial to the pubic tubercle (Fig 4). On ultrasound, the inguinal canal can be traced along its path, starting at the internal inguinal ring and extending to the external inguinal ring (Fig 5).

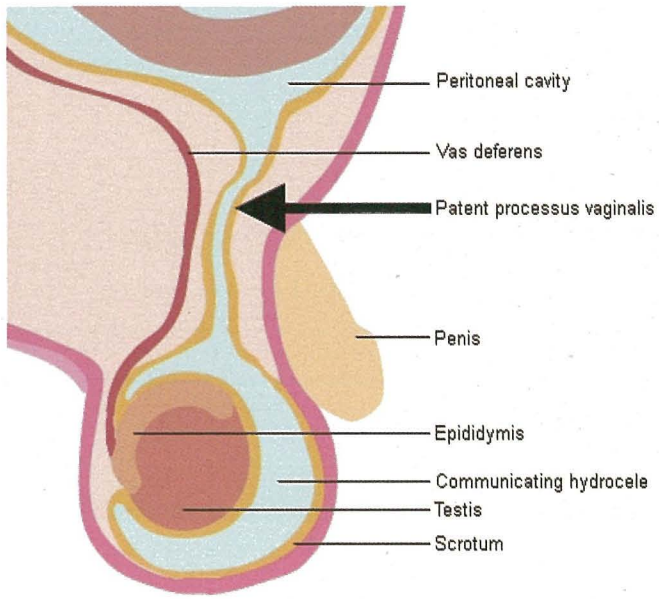

Figure 3. Diagram showing a patent processus vaginalis (arrow) communicating the peritoneal cavity with the tunica vaginalis; this is called a communicating hydrocoele.

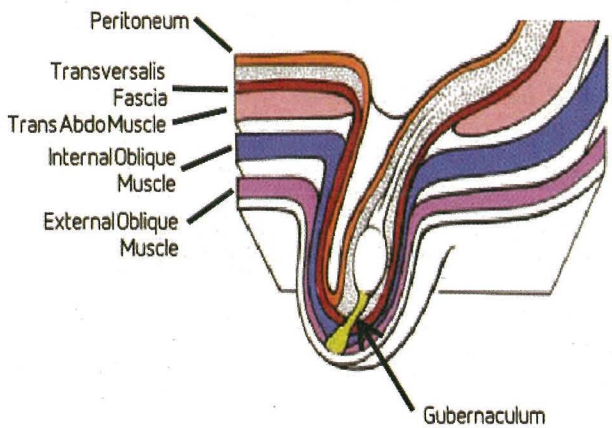

Figure 2. The gubernaculum is attached to the inferior pole of the gonad proximally and into the labroscrotal fold inferiorly. It shortens from the 7th week of gestation onwards and pulls the gonad inferiorly. In males, the testis descends into the scrotum. Due to the attachment of the gubernaculum to the uterus in females, the ovary halts next to the uterus and the distal gubernaculum forms the round ligament. All abdominal wall layers extend along the gubernaculum and around the testis to form the scrotum in males. The path through which the testis and round ligament pass represents the inguinal canal.

INGUINAL HERNIAS

An indirect inguinal hernia results from the passage of intraabdominal contents into the inguinal canal through the internal inguinal ring. Whereas a direct inguinal hernia passes directly through the abdominal wall layers and does not follow the inguinal canal. An indirect inguinal hernia therefore passes lateral to the inferior epigastric vessels while a direct inguinal hernia courses medial to them (Fig. 6).

Direct and indirect inguinal hernias are usually more evident when the patient increases his/her intraabdominal pressure (e.g. during Valsalva manoeuvre or in the standing position). Consequently, dynamic ultrasound examination at rest, during Valsalva and in the standing position are necessary to detect an

DIRECT AND INDIRECT INGUINAL HERNIAS ARE USUALLY MORE EVIDENT WHEN THE PATIENT INCREASES HIS/HER INTRA-ABDOMINAL PRESSURE

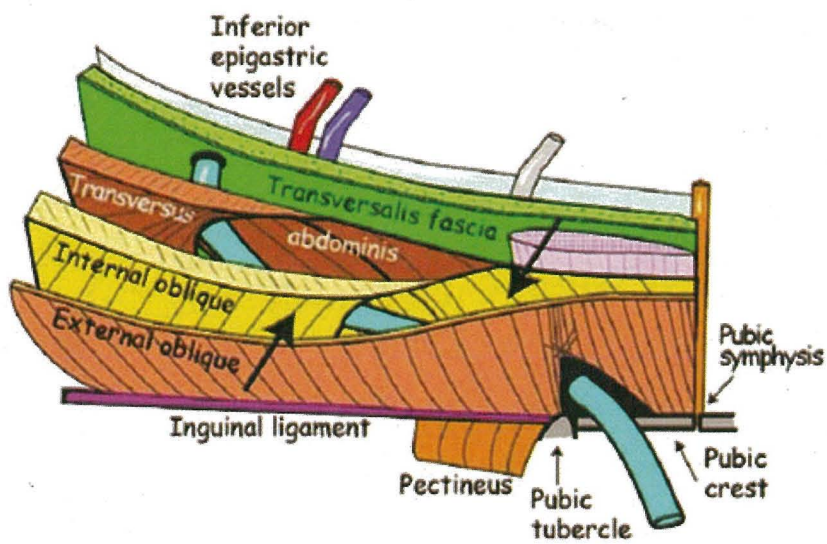

Figure 4. Anatomy of the inguinal canal (arrows). The anterior wall is formed by the external and internal oblique muscle aponeuroses and the posterior wall is composed of the transversus abdominis aponeurosis and the conjoint tendon; the latter is formed by fusion of the distal rectus abdominis tendon with the proximal adductor longus tendon.

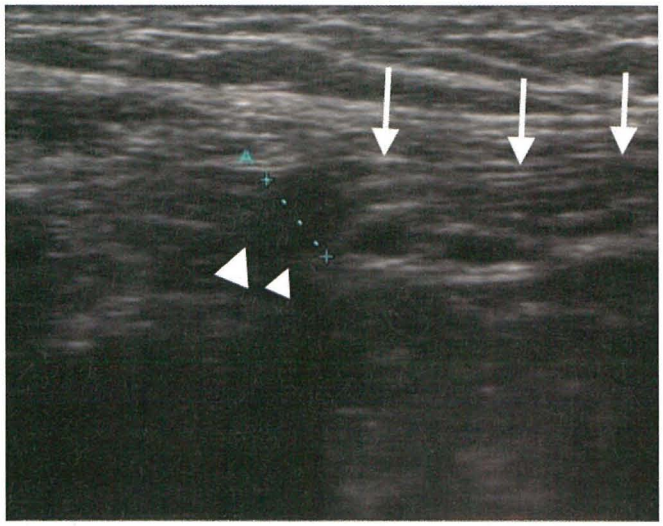

Figure 5. Ultrasound scan parallel to the course of the inguinal canal, showing the internal inguinal ring (arrowheads) and the inguinal canal (arrows) with its contents.

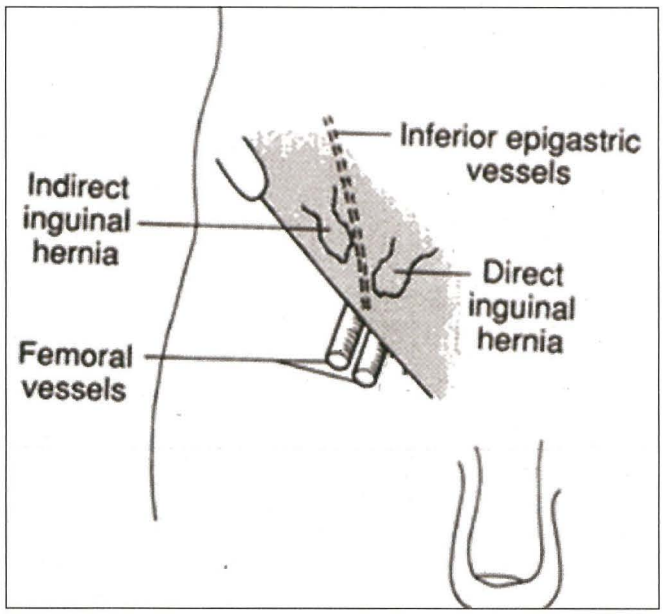

Figure 6. A direct inguinal hernia passes lateral to the inferior epigastric vessels, while a direct inguinal hernia courses medial to them.

inguinal hernia since a hernia may be fully reduced at rest. In addition, dynamic examination will help distinguish reducible from incarcerated hernias, since the latter do not reduce even on compression with the probe (Fig 7). Thickening of the contents of the hernial sac and associated fluid collections are signs of strangulation of the hernia contents (Fig 8). Strangulation may also be noted through the absence of blood flow on colour Doppler ultrasound examination.

The more common complications of surgical hernia repair include seromas, haematomas and abscesses at the site of repair. These are readily detected by ultrasound (Fig 9). Abscesses tend to appear in the late post-operative period (usually after 30 days) and are accompanied by clinical signs of infection. A further post-operative complication of hernia is repair is hernia recurrence, which is also readily detected by ultrasound.

To be continued...

THE MORE COMMON COMPLICATIONS OF SURGICAL HERNIA REPAIR INCLUDE SEROMAS, HAEMATOMAS & ABSCESSES AT THE SITE OF REPAIR

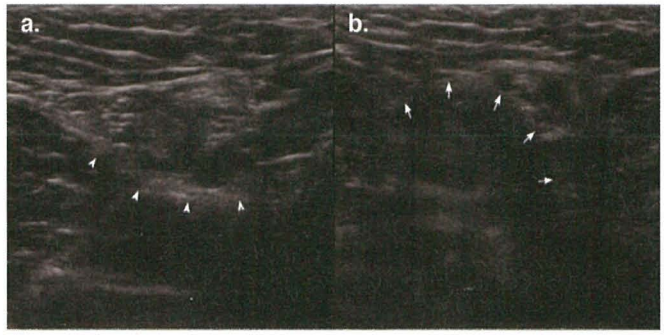

Figure 7. Ultrasound scan of an indirect inguinal hernia showing the inguinal canal at rest (a.) and during Valsalva maneouvre. b. Note the expansion of the inguinal canal that occurs with increased intraabdominal pressure (arrows).

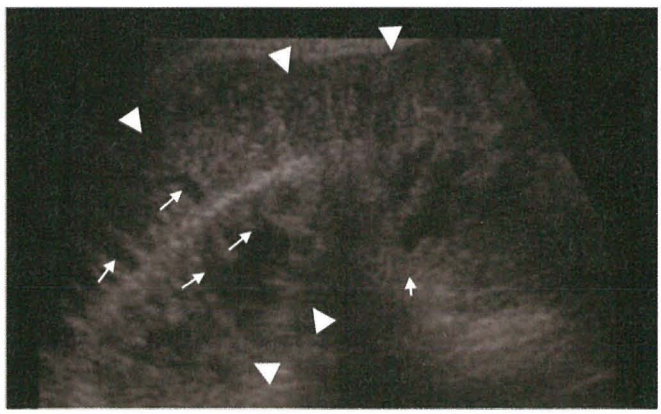

Figure 8. Ultrasound scan showing a thickened loop of small bowel (arrowheads) in the inguinal canal that did not alter with Valsalva manoeuvre and did not reduce on compression. Also note the thickened mucosal folds (arrows); the thickened bowel wall and bowel loops are indicative of hernia strangulation.

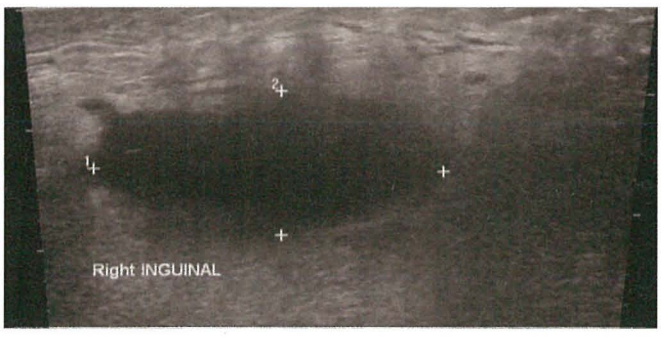

Figure 9. Ultrasound scan showing a fluid collection (calipers) at the site of a hernia repair in the early post-operative period.

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Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. DuoResp® Spiromax® 320/9: Only to be used as maintenance therapy. Adults (18 years and older): 1 inhalation twice daily (maximum of 2 inhalations twice daily). **COPD:** Adults (18 years and older): 1 inhalation twice daily. Elderly patients (≥65 years old): No special requirements. Patients with renal or hepatic impairment: No data available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions and warnings:** If treatment is ineffective, or exceeds the highest recommended dose, medical attention must be sought. Patients with sudden and progressive deterioration in control of asthma or COPD should undergo urgent medical assessment. Patients should have their rescue inhaler available at all times. The reliever inhalations should be taken in response to symptoms and are not intended for regular prophylactic use, e.g. before exercise. For such, a separate rapid-acting bronchodilator should be considered. Patients should not be initiated during an exacerbation. Serious asthma- related adverse events and exacerbations may occur. If asthma symptoms remain uncontrolled or worsen, patients should continue treatment and seek medical advice. If paradoxical bronchospasm occurs, treatment should be discontinued immediately. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Systemic effects may occur, particularly at high doses prescribed for long periods, e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Potential effects on bone density should be considered, particularly in patients on high doses for prolonged periods that have co- existing risk factors for osteoporosis. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress, e.g. severe infections or elective surgery. Treatment should not be stopped abruptly. Transfer from oral steroid therapy to a budesonide/formoterol fumarate fixed-dose combination may result in the appearance of allergic or arthritic symptoms which will require treatment. In rare cases, tiredness, headache, nausea and vomiting can occur due to insufficient glucocorticosteroid effect and temporary increase in the dose of oral glucocorticosteroids may be necessary. To minimise risk of oropharyngeal candida infection patients should rinse mouth with water. Administer with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, or severe cardiovascular disorders. The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways. Additional blood glucose controls should be considered in diabetic patients. Hypokalaemia may occur at high doses. Particular caution is recommended in unstable or acute severe asthma. Serum potassium levels should be monitored in these patients. As with other lactose containing products the small amounts of milk proteins present may cause allergic reactions. **Interactions:** Concomitant treatment with potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administration should be as long as possible. Not recommended with beta adrenergic blockers (including eye drops) unless compelling reasons. Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), MAOIs and TCAs can prolong the QTc-interval and increase the risk of ventricular arrhythmias. L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance. Concomitant treatment with MAOIs, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions. Patients receiving anaesthesia with halogenated hydrocarbons have an elevated risk of arrhythmias. Hypokalaemia may increase the disposition towards arrhythmias in patients taking digitalis glycosides. **Pregnancy and lactation:** Use only when benefits outweigh potential risks. Budesonide is excreted in breast milk; at therapeutic doses no effects on child are anticipated. **Effects on ability to drive and use machines:** No or negligible influence on the ability to drive and use machines. **Adverse reactions:** Serious: Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction, Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, hypokalaemia, hyperglycaemia, aggression, psychomotor hyperactivity, anxiety, sleep disorders, depression, behavioural changes, cataract and glaucoma, tachycardia, cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles, angina pectoris, prolongation of QTc-interval, variations in blood pressure, bronchospasm and paradoxical bronchospasm. Common: Candida infections in the oropharynx, headache, tremor, palpitations, mild irritation in the throat, coughing and hoarseness. Consult the Summary of Product Characteristics in relation to other side effects. **Overdose:** An overdose of formoterol may lead to: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc- interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. **Marketing Authorisation Numbers:** EU/1/14/ 920/001 & EU/1/14/920/004. **Marketing Authorisation Holder:** Teva Pharma BV, Computerweg 10, 3542 DR Utrecht, The Netherlands. **Date of Preparation:** March 2017. **Job Code:** TEV03/17 J6585. **References:** 1. MDEA 2015. Available at: http://www canontradeshows.com/expo/awards/awards. Accessed: March 2016. 2. DuoResp Spiromax® Summary of Product Characteristics. Available at: http://www.medicinesauthority.gov.mt/medicinesdatabase. Accessed: March 2016. *DuoResp Spiromax® is licensed for use in adults 18 years of age and older only. 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