

# THE SYNAPSE

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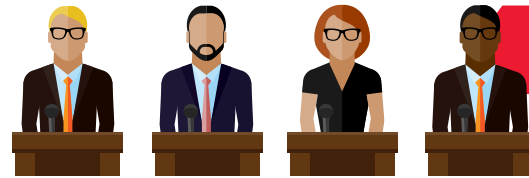
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# THE UPCOMING MALTESE GENERAL ELECTION PRIDE & PREJUDICE



EDITORIAL

Media has recently reported that the forthcoming Maltese election will be held around March 2018 (or earlier). One does not need to be an expert in history to foresee that the temperament of the government during the next 11 months or so 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 whopping €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...

*Pan 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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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. **DOSEAGE:** 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 100mg 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. 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Combination with sulphonylurea: Common: hypoglycaemia, dizziness, headache, diarrhoea, nausea, hypoglycaemia. Combination with thiazolidinedione: Common: weight increase, oedema peripheric. Combination with insulin: Common: decreased blood glucose, headache, dizziness, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, nausea, hypoglycaemia, asthma. 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, Emley Business Park, Canterbury, UK. **MARKETING AUTHORISATION NUMBERS:** EU/1/02/741/003. **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 21226072. 2017-MT-CAL-DIG-MAR 2017

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Acute or chronic disease which may cause tissue hypoxia (e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, anaemia, haematuria). **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 in acute worsening of renal function, or cardiovascular or cerebrovascular disease. Metformin accumulation occurs in acute worsening of renal function and increases the risk of lactic acidosis. eGFR should be assessed before treatment initiation and renewed 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 restarted 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 the maximal 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. If acute hypoglycaemia is confirmed in combination with a 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 oral antidiabetics (gliflozins, glitazones, metformin), antidiabetic dipeptidyl peptidase-4 inhibitors or with oral contraceptives 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, combined contrast agents, calcium active substances (e.g. chelators) and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hypoglycaemic activity (e.g. glycoamides, 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)-2 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:** Most cases (<1/1000 to <1/10000) 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 peripheric, very rare (<1/10,000): URTI, nasopharyngitis, Metformin monotherapy: Very common (>1/10): nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, common: taste disturbance, hypoglycaemia, dizziness, headache, dizziness, nausea, hypoglycaemia, uncommon: tremor, headache, dizziness, nausea, hypoglycaemia, uncommon: fatigue. Combination with metformin and sulphonylurea: Common: hypoglycaemia, dizziness, nausea, hypoglycaemia, asthma, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, dizziness, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of Adverse Reactions, please refer to the SmPC. **LEGAL CATEGORY:** POM. **PACK SIZES:** 28, 60 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Emley Business Park, Canterbury, UK. **MARKETING AUTHORISATION NUMBERS:** EU/1/02/741/003. **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 21226072. 2016-MT-EUC-12-DEC 2016

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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<sup>1</sup>. 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)<sup>2</sup>. 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<sup>3</sup>, 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%<sup>4,5</sup>. 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<sup>5</sup>.

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<sup>6</sup> and C<sup>7</sup>, 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<sup>8</sup>. 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<sup>9</sup>.

## 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<sup>10</sup>. 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)<sup>11</sup>.

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<sup>12</sup>, 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<sup>13</sup>. Gender does not appear to be a factor, with infection rates being similar for boys and girls.

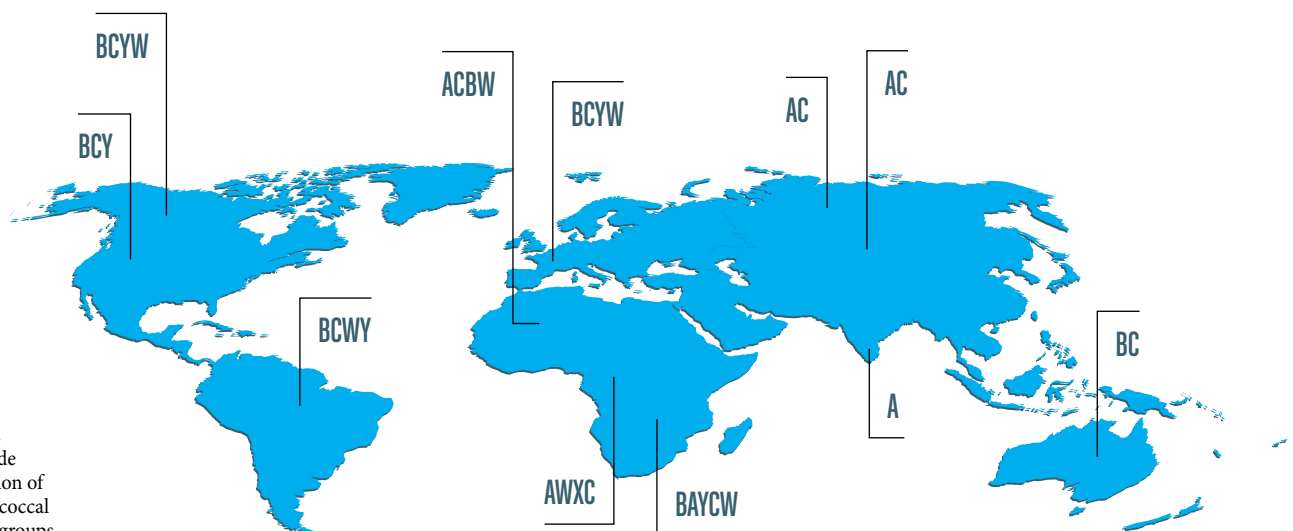
A comprehensive epidemiological review of IMD in Malta<sup>14</sup> has confirmed an overall incidence rate for all types of meningococcal disease in 2000-2012 of 1.7/100,000, well above the European average of 1.1/100,000 for the same time period. The individual incidence rate was 0.99 and 0.3/100,000 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<sup>14</sup>. 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<sup>15</sup>. 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<sup>16</sup>.

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<sup>17</sup>, 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<sup>18</sup>.

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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to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta<sub>2</sub>-agonist, if patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. For COPD: One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** Hypersensitivity to the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** **Pregnancy:** No adequate data available. **Lactation:** insufficient information available. **Fertility:** There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of

general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom. **Marketing Authorisation Numbers:** EU/113/896/001-6. **DATE OF PREPARATION:** December 2013. In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)

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Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: [www.medicinesauthority.gov.mt/adrportal](http://www.medicinesauthority.gov.mt/adrportal)

Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): <https://yellowcard.mhra.gov.uk/>

**References:** 1. Relvar Ellipta Summary of Product Characteristics, GlaxoSmithKline, 2016. MLT\_GIB/FF/0003/17 Date of preparation: January 2017



In practice, they proved effective in isolated outbreaks involving single strains in Norway in 1990 with 57.2% protection<sup>19</sup>, Cuba in 1990 with 83% efficacy<sup>20</sup>, and Normandy, France in 2003<sup>21</sup>. 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<sup>22</sup>.

Table 1. Components of 4CMenB vaccine

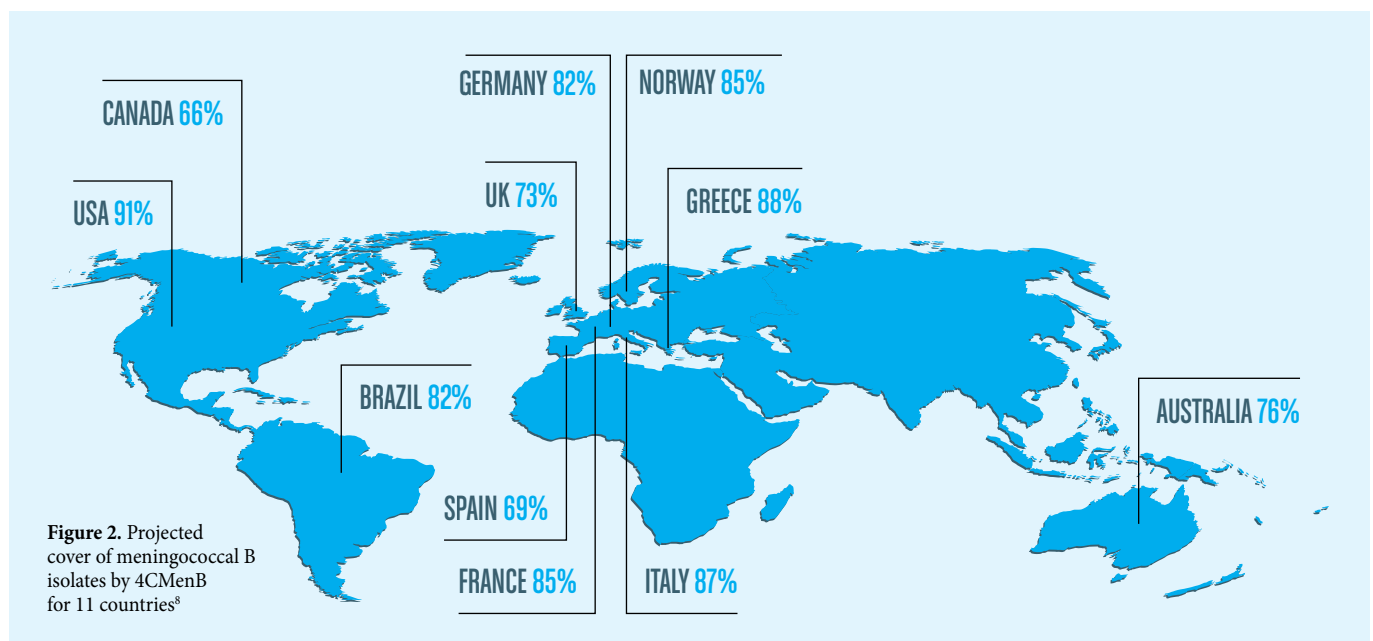
Component	Action
NadA	Promotes adherence to human epithelial cells
NHBA	Binds heparin, prolonging bacterial survival in blood
fHbp	Binds factor H, allowing bacterial survival in blood
NZ PoA 1.4	Induces strain specific bactericidal response

**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<sup>23</sup>. 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<sup>24</sup>. 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)<sup>9</sup>.

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<sup>25</sup>. 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<sup>26</sup>.



## 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<sup>27</sup>. 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<sup>28</sup>.

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<sup>29</sup>.

## 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

I would like to thank Dr David Pace for reviewing the manuscript.

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Just last month, Jane was a prisoner in her own home.



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**WELLBUTRIN XR** – Abbreviated Prescribing Information: *Please refer to full Summary of Product Characteristics (SmPC) before prescribing.* **TRADE NAME:** Wellbutrin XR modified release tablets. **COMPOSITION:** Bupropion Hydrochloride 150mg and 300mg. **INDICATIONS:** Treatment of major depressive episodes. **POSOLGY AND METHOD OF ADMINISTRATION:** Wellbutrin XR tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse events including seizures. **Adults:** The recommended starting dose is 150mg once daily; if no improvement is seen after 4 weeks the dose may be increased to 300mg once daily. There should be an interval of at least 24 hours between successive doses. **Children and Adolescents:** Not indicated for use in children or adolescents aged less than 18 years. **Elderly Patients:** Same as adults but with greater sensitivity in some elderly individuals. **Hepatic and renal impairment:** 150mg once a day. **Discontinuing therapy:** A tapering off period may be considered. **Overdose:** Symptoms including drowsiness, loss of consciousness and/or ECG changes and rarely deaths even with large overdoses. **CONTRAINDICATIONS:** Hypersensitivity to bupropion or any of the excipients; co-administration with other medicinal products containing bupropion as the incidence of seizures is dose-dependent; current seizure disorder or history of seizures; known CNS tumor; withdrawal from alcohol or any medicinal product known to be associated with the risk of seizures on withdrawal; severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **SPECIAL WARNINGS AND PRECAUTIONS:** Do not exceed the recommended dose of Wellbutrin XR especially in patients who have predisposing factors for seizures since the risk of seizures is dose-related. Not recommended/discontinued in patients who experience a seizure during treatment. Careful monitoring during the first weeks of treatment/dose changes/in patients with history of suicide-related events prior to treatment; discontinuation should be considered in cases of severe and sudden onset of suicidal ideation/behaviour. Wellbutrin XR should be discontinued promptly if patients experience hypersensitivity reactions during treatment; Use with caution in patients with hepatic and renal impairment. **INTERACTIONS:** Concomitant use with MAOI's is contraindicated; The dose of certain antidepressants, anti-psychotics, beta-blockers, SSRI's and Type 1C antiarrhythmics should be reduced when given concomitantly with Wellbutrin XR; Use with caution with cyclophosphamide and ticlopidine, carbamazepine, phenytoin, ritonavir, tamoxifen,

valproate, levodopa or amantidine, alcohol and nicotine transdermal system. **ADVERSE EVENTS:** *Very Common:* Insomnia, headache, dry mouth, gastrointestinal disturbance including nausea and vomiting; *Common:* Hypersensitivity reactions such as urticaria, anorexia, agitation, anxiety, tremor, dizziness, taste disorders, visual disturbance, tinnitus, increased blood pressure (sometimes severe), flushing, abdominal pain, constipation, rash, pruritus, sweating, fever, chest pain and asthenia. *Not known:* suicidal ideation and suicidal behaviour. Refer to the SPC for a full list of adverse events. **PREGNANCY AND LACTATION:** Not recommended. **ABILITY TO DRIVE AND USE MACHINES:** Use with caution. **PRESENTATIONS:** Wellbutrin XR 150mg and 300mg x 30 tablets. **LEGAL CATEGORY:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, UK. **Marketing Authorisation Number:** MA 302/00101-2. **Date of preparation:** August 2016  
In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)

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Job No: MLT\_GIB/BHC/0002/16a Prepared: October 2016



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micronized purified flavonoid fraction



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**COMPOSITION:** Micronized, purified flavonoid fraction 500 mg: 450 mg diosmin; 50 mg flavonoids expressed as hesperidine. **INDICATIONS:** Treatment of symptoms related to venolymphatic insufficiency (heavy legs, pain, early morning restless legs). Treatment of functional symptoms related to acute hemorrhoidal attack. **DOSAGE AND ADMINISTRATION:** Usual dosage: 2 tablets daily in two divided doses, midday and evening at meal times. Acute hemorrhoidal attack: 6 tablets per day for the first 4 days, then 4 tablets per day for 3 days. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS :** The administration of this product for the symptomatic treatment of acute hemorrhoids does not preclude treatment for other anal conditions. If symptoms do not subside promptly, a proctological examination should be performed and the treatment should be reviewed. **INTERACTION(S):** No interactions have been reported to-date. **PREGNANCY:** No teratogenic effects have been shown in several studies and no adverse effect have been reported in human. **LACTATION:** In the absence of data on excretion in milk, treatment should be avoided during breast-feeding. **FERTILITY:** In animals, experimental studies did not show any teratogenic effect. **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. **PHARMACODYNAMIC PROPERTIES:** Vascular 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. **LES LABORATOIRES SERVIER**, 50 rue Carnot, 92284 Suresnes cedex France. [www.servier.com](http://www.servier.com)  
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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)<sup>1</sup> 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<sup>2</sup>.

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*<sup>3</sup> 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<sup>4</sup>. 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<sup>2</sup>. 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<sup>2</sup>. 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<sup>5</sup>. In particular, as Marmot emphasizes “The mother’s education is a much stronger predictor of infant mortality than is household income or wealth”<sup>3</sup>.

- 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<sup>3</sup>.
- 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<sup>3</sup>. 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)<sup>6</sup>.

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<sup>7</sup>. 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)<sup>8</sup>. Indeed, in 2013, the proportion of early school leavers was less in females compared to males (18% compared to 23%)<sup>7</sup>.

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<sup>9</sup>, 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.”<sup>3</sup>

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<sup>3</sup>.

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<sup>3</sup>.

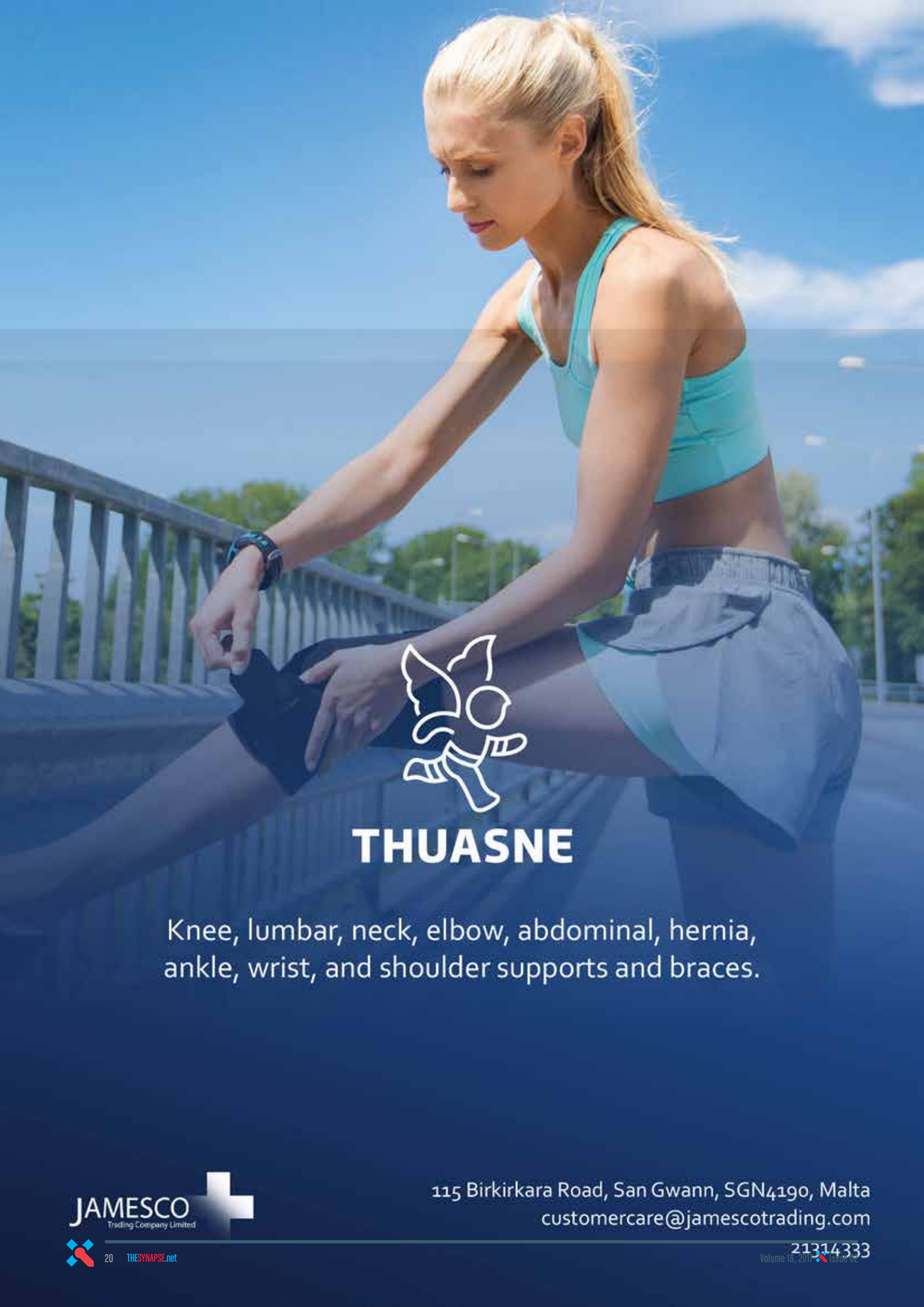
### **How does all this affect busy medical practitioners who are not expected to be social workers and who have rarely been educated in social issues as they affect health?**

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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# THUASNE

Knee, lumbar, neck, elbow, abdominal, hernia, ankle, wrist, and shoulder supports and braces.

# THE MANGA GUIDE TO BIOCHEMISTRY

**Author:** Masaharu Takemura  
**Illustrator:** Kikuyaro  
**Producer:** Office Sawa  
**Publisher:** No Starch Press  
**Paperback:** 272 pages  
**English Release Date:** November, 2011  
**Print ISBN-13:** 978-1-59327-276-0

MICHELLE MUSCAT

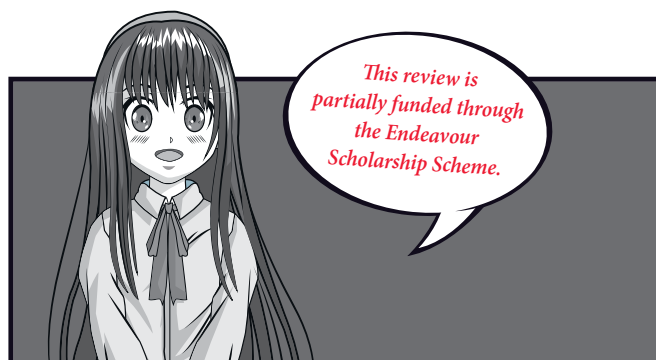


**T**he Manga Guide to Biochemistry” offers a unique take on more complex biochemical processes, presenting these in diagrammatic and intuitive forms, that would especially appeal to audiences who enjoy manga, as well as those who would potentially consider taking up a career in biochemistry, or related 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”<sup>1</sup> 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<sup>2-6</sup>. 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 Bencini reporting for duty, Sir’

## A DOCTOR'S LIFE IN THE ARMY

**F**or this issue, MARIKA AZZOPARDI meets up with COLONEL CHEVALIER DR RAYMOND BENČINI 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 Bencini 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



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

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.

### 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



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

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!

**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



Ramona, Alexander, Tara, Marlena and Dr Bencini in a visit to Tai O, the sea village on stilts in Lantau, Hong Kong

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.

**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. ❄️

**I READ THE SYNAPSE BECAUSE...**

It keeps me updated about medicine.



# ULTRASOUND OF THE INGUINAL CANAL

## PART I

PIERRE VASSALLO

**U**ltrasound 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 7<sup>th</sup> 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 labrosrotal fold; the labrosrotal 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

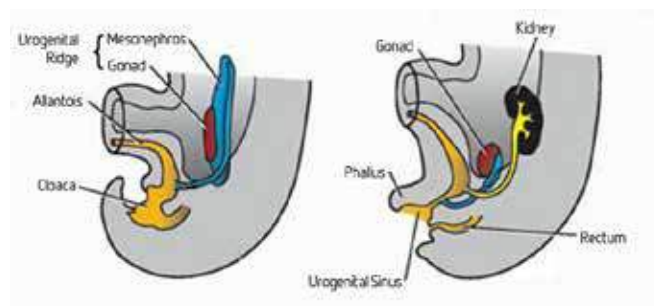


Figure 1. The kidney and gonad develop from a common structure, the urogenital ridge, that is located next to the structures that will form the lower spine in the embryo. The inner part of the urogenital ridge forms the gonad that descends into the pelvic/scrotal area, while the lateral part forms the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

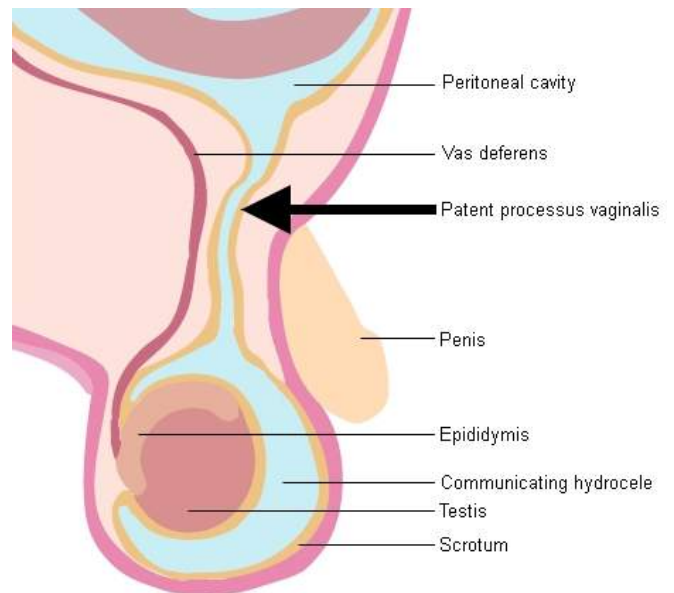


Figure 3. Diagram showing a patent processus vaginalis (arrow) communicating the peritoneal cavity with the tunica vaginalis; this is called a communicating hydrocoele.

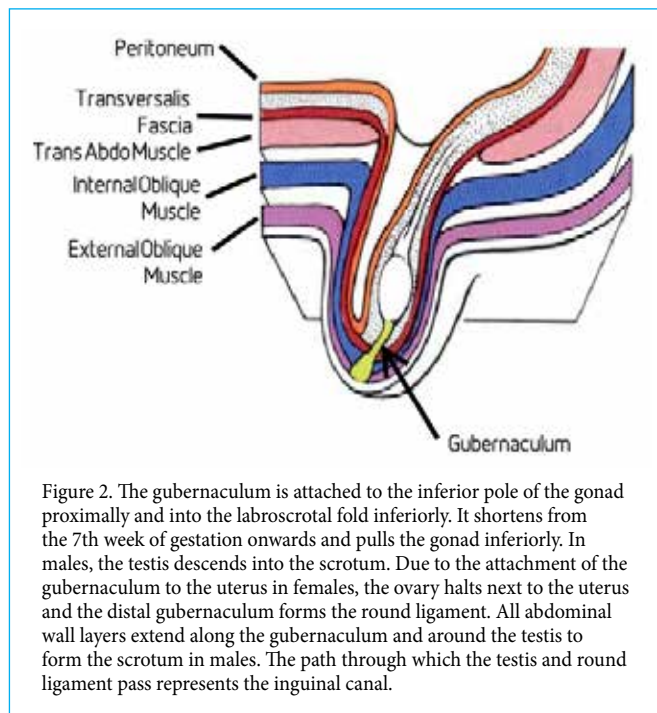


Figure 2. The gubernaculum is attached to the inferior pole of the gonad proximally and into the labrosrotal fold inferiorly. It shortens from the 7th week of gestation onwards and pulls the gonad inferiorly. In males, the testis descends into the scrotum. Due to the attachment of the gubernaculum to 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  
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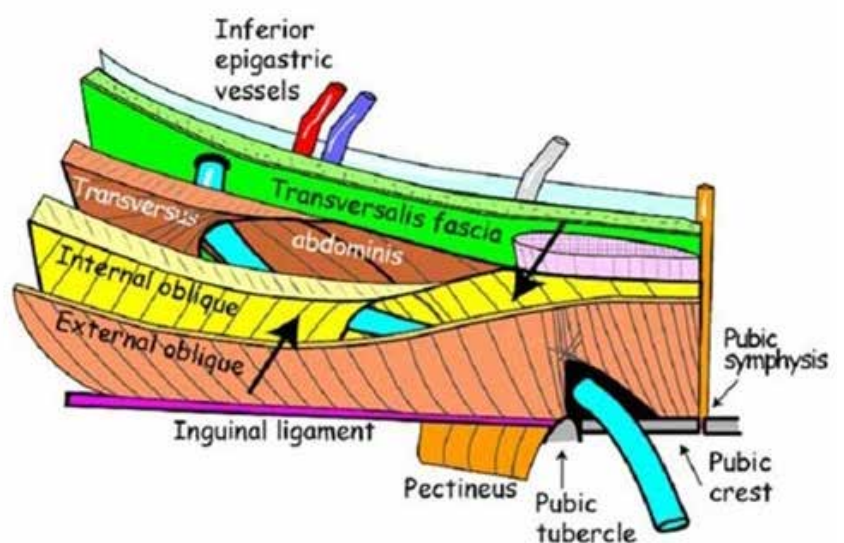


Figure 4. Anatomy of the inguinal canal (arrows). The anterior wall is formed by the external and internal oblique muscle aponeuroses and the posterior wall is composed of the transversus abdominis aponeurosis and the conjoint tendon; the latter is formed by fusion of the distal rectus abdominis tendon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



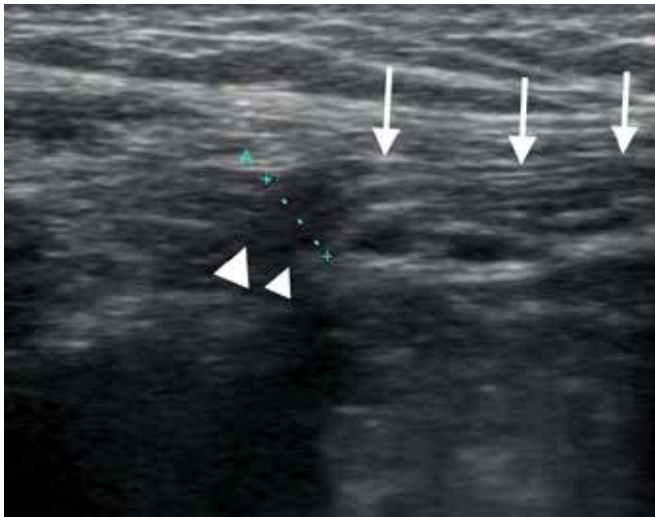


Figure 5. Ultrasound scan parallel to the course of the inguinal canal, showing the internal inguinal ring (arrowheads) and the inguinal canal (arrows) with its contents.

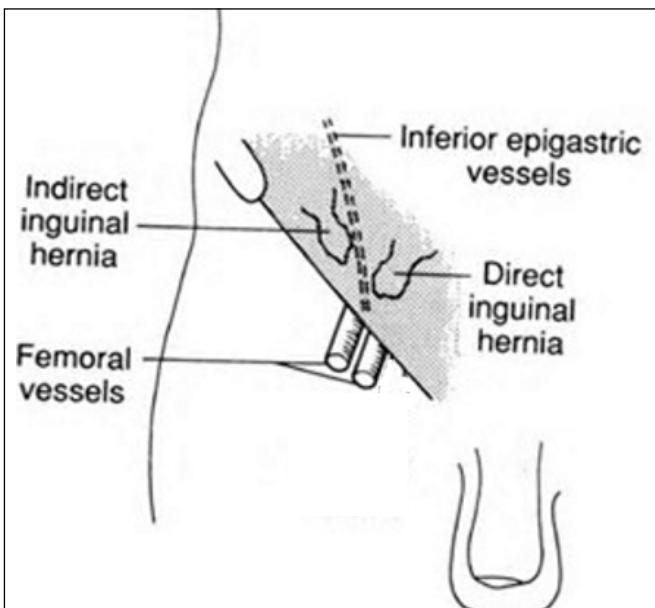


Figure 6. A direct inguinal hernia passes lateral to the inferior epigastric vessels, while a direct inguinal hernia courses medial to them.

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

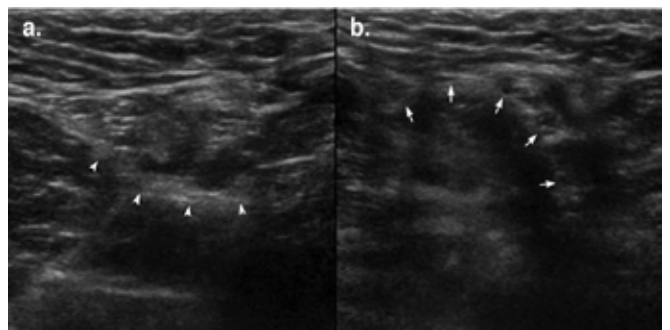


Figure 7. Ultrasound scan of an indirect inguinal hernia showing the inguinal canal at rest (a.) and during Valsalva manoeuvre. b. Note the expansion of the inguinal canal that occurs with increased intraabdominal pressure (arrows).

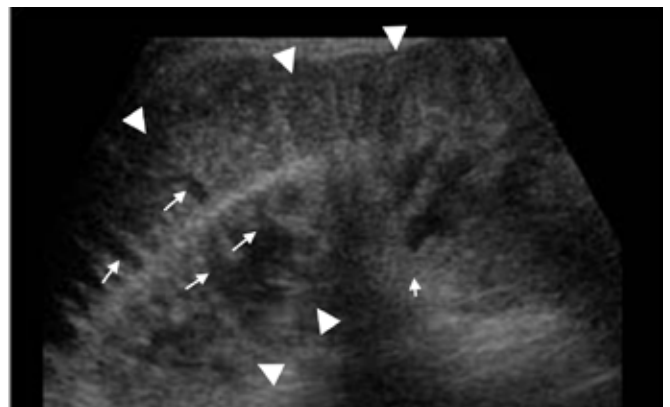


Figure 8. Ultrasound scan showing a thickened loop of small bowel (arrowheads) in the inguinal canal that did not alter with Valsalva manoeuvre and did not reduce on compression. Also note the thickened mucosal folds (arrows); the thickened bowel wall and bowel loops are indicative of hernia strangulation.

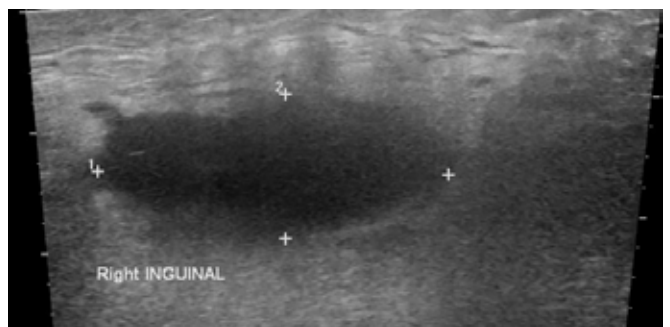


Figure 9. Ultrasound scan showing a fluid collection (calipers) at the site of a hernia repair in the early post-operative period.



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320mcg/9mcg

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**Please refer to the Summary of Product Characteristics (SmPC) for full details of the Prescribing Information.** DuoResp<sup>®</sup> Spiromax<sup>®</sup> (budesonide/formoterol) 160 micrograms/4.5 micrograms inhalation powder and DuoResp<sup>®</sup> Spiromax<sup>®</sup> (budesonide/formoterol) 320 micrograms/9 micrograms inhalation powder Abbreviated Prescribing Information. **Presentation:** DuoResp<sup>®</sup> Spiromax<sup>®</sup> 160/4.5; Each delivered dose contains 160 micrograms of budesonide and 4.5 micrograms of formoterol fumarate dihydrate. This is equivalent to a metered dose of 200 micrograms budesonide and 6 micrograms of formoterol fumarate dihydrate. DuoResp<sup>®</sup> Spiromax<sup>®</sup> 320/9; Each delivered dose contains 320 micrograms of budesonide and 9 micrograms of formoterol fumarate dihydrate. This is equivalent to a metered dose of 400 micrograms budesonide and 12 micrograms of formoterol fumarate dihydrate. Inhalation powder. **Indications:** Treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta - adrenoceptor agonist) is appropriate. COPD: Symptomatic treatment of patients with severe COPD (FEV<sub>1</sub> <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators. **Dosage and administration:** Not indicated for use in children, 12 years of age and younger, or adolescents, 13 to 17 years of age. **Asthma:** Not intended for the initial management of asthma. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of  $\beta$  adrenoceptor agonists and/or corticosteroids by individual inhalers should be prescribed. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is achieved titrate to the lowest effective dose, which could include once daily dosing. DuoResp<sup>®</sup> Spiromax<sup>®</sup> 160/4.5: DuoResp<sup>®</sup> Spiromax<sup>®</sup> maintenance therapy – regular maintenance treatment with a separate reliever inhaler. Adults (18 years and older): 1-2 inhalations twice daily (maximum of 4 inhalations twice daily). DuoResp<sup>®</sup> Spiromax<sup>®</sup> maintenance and reliever therapy – regular maintenance treatment and as needed in response to symptoms: should be considered for patients with: (i) inadequate asthma control and in frequent need of reliever medication (ii) previous asthma exacerbations requiring medical intervention. Adults (18 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. 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<sup>®</sup> Spiromax<sup>®</sup> 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 ( $\geq 65$  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:** TEV03/17/6585. **References:** 1. MDEA 2015. Available at: <http://www.canontradeshow.com/expo/awards/awards>. Accessed: March 2016. 2. DuoResp Spiromax<sup>®</sup> Summary of Product Characteristics. Available at: <http://www.medicinesauthority.gov.uk/medicinesdatabase>. Accessed: March 2016. "DuoResp Spiromax<sup>®</sup>" is licensed for use in adults 18 years of age and older only. Teva Pharmaceuticals Europe BV, Piet Heinkade 107, 1019 GM Amsterdam, The Netherlands.

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