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THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

- ✦ New Safety Information on Azithromycin
- ✦ A Review of the Impact of Social Determinants on Health in Malta
- ✦ CVD Challenge - Win with Servier

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PRESENTATION: Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. **Method of administration** For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. **Asthma:** Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy

instituted. **Paradoxical bronchospasm:** As with other inhalation therapy, administration of Ultibro Breezhaler may result in paradoxical bronchospasm which can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. **Narrow-angle glaucoma:** No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. **Urinary retention:** No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. **Cardiovascular effects:** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). **Hypokalaemia:** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. **Hyperglycaemia** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. **Pregnancy and Lactation:** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or

non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, dyspepsia, dental caries, bladder obstruction and urinary retention, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest pain, oropharyngeal pain including throat irritation, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, gastroenteritis tachycardia, palpitations, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY: POM PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003, EU/1/13/862/007. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O. Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872

2016-MT-ULT-10-NOV-2016

References

1. Wedzicha JA, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.
2. Novartis Europharm Ltd. Ultibro Breezhaler Summary of product characteristics.

NOVARTIS

EQUAL OPPORTUNITY... MORE THAN ANYTHING MEANS A GREAT EDUCATION ELEARNING VS TRADITIONAL FACE-TO-FACE INTERACTION

In a 1980 interview, Steve Jobs (1955 – 2011), an American entrepreneur, businessman, inventor and industrial designer once stated that *'Equal opportunity to me more than anything means a great education.'* This proves to be a most convenient introduction to this editorial which will discuss the relevance of continuing medical education and eLearning for healthcare professionals.

Let's face it. Educators face a number of key challenges in the provision of continuing medical education programmes. To name a few, the World Federation of Medical Education [<http://wfme.org/>] mentions inadequate leadership, insufficient resources, lack of programme supervision and resistance to change. In essence, one might well say that the main challenge is the development of modules which are easily accessible [including cost], of good quality [including ease-of-use], and yet, flexible enough to fit in the lifestyle of prospective participants.

The World Organization of Family Doctors [www.globalfamilydoctor.com/] and the World Federation of Medical Education particularly recommend flexibility and adaptability in the provision of continuing medical education programmes. Indeed, a lack of flexible training opportunities have been signalled as reasons leading to medical brain drain. In keeping with this, self-directed learning is shaping itself as a robust pillar of lifelong learning, alongside traditional taught curricula.

It only makes sense that for continuing medical education programmes to succeed, these need to include eLearning modules. These eLearning modules need to be spearheaded by competent and experienced stakeholders who have access and are willing to manage the required [1] manpower (including content built-up) and [2] technological infrastructure (including the development of a stable and robust delivery platform) to be able to implement and disseminate such eLearning modules in an efficient and effective way. Quality assurance is the linchpin of the entire process, in view of the changing nature of healthcare provision and increasing expectations of participants and patients alike. Such total quality management should be monitored through continuous checks and

balances ingrained in the process, preferably by an independent body. This should obviously include periodic data mining exercises to perform feedback analysis.

The challenge relating to manpower should not be underestimated. It is true that candidates eligible for continuing medical education have increased over the years. This obviously entails a significant burden on the provision of education since more tutors are required to teach and supervise students. And the future of traditional taught curricula within the context of local continuing medical education does not look any rosier, since it would seem that manpower resources will be stretching even more in the immediate future. Let me elaborate this further. As discussed in the previous editorial, the recent agreement between the Maltese Ministry of Health and the Queen Mary University of London relating to the opening of a medical school in Gozo foresees the opening of a campus of the Barts and the London School of Medicine and Dentistry. The Maltese government confirmed that the first students will be accepted in September 2017. This will stress the current manpower resources, specifically relating to the provision of continuing medical education, even more. In keeping with this, during the last months, medical students have consistently voiced their concern that the privatisation of medical education in Malta would dilute the medical school's education resources.

The development of accredited eLearning modules will, logically, offset any manpower shortages ...

In view of the above, all stakeholders need to roll up their sleeves, adapt [more] to the concept of eLearning and develop eLearning modules, similar to the ones currently hosted by the Malta Medical Foundation Programme [<http://fpmalta.com/foundation-programme/e-learning/>].

Ending with Steve Job's challenging remark, the provision of free-of-charge [or cheap] eLearning modules, accredited by professional bodies, will surely provide an equal opportunity to all concerned to access great education. 🇲🇹

Pan Ellul



Cover: Medical staff at work in a Maltese hospital, circa 1960s-1970s.

Photo Credit: Photograph by Wilfred Flores, courtesy of Anton Borg Olivier. Wilfred Flores (1912-1981) was a skilled forensic photographer and calligraphy expert. He was actively involved in the setting up of early Maltese photography groups and the teaching of photography.

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Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** The 92 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV₁<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The 184 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** For Asthma: One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary

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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 beta₂-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 beta₂-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/1/13/886/001-6. **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
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/FFT/0003/17 Date of preparation: January 2017



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Dr Michelle Muscat MD, MRCS(Ed), MSc, PG Dip, FRCPath is currently in her fourth year reading for a full time PhD. She is a fellow of the Royal College of Pathologists, in chemical pathology, and harbours a strong interest in biochemical laboratory science.



Dr Michelle Deguara MD is a Specialist Trainee in Public Health Medicine and an MSc Public Health candidate. Her main interests are health promotion and disease prevention, health literacy and inequalities in health. The co-authors of the article are Drs Kathleen England and Natasha Azzopardi Muscat.



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A REVIEW OF THE IMPACT OF SOCIAL DETERMINANTS ON HEALTH IN MALTA

ABSTRACT

Socioeconomic conditions such as income and education have been demonstrated to be strong determinants of health status. This issue has been little researched in Malta and consequently has not made it to the top of the health policy agenda. This article reviews locally available evidence on the social determinants of health. Findings confirm that the inverse relationship between life-expectancy and chronic health conditions and lifestyle behaviours and socioeconomic status demonstrated in other countries, also exists in Malta. Greater awareness amongst health professionals and further research on the social determinants of health are necessary as rising income inequality and multi-ethnicity are both becoming important phenomena in Malta's sociodemographic evolution. Public health approaches to tackle illness and wellbeing need to go beyond traditional educational campaigns and must focus on measures that support a more equitable and just society.

INTRODUCTION

The World Health Organisation (WHO) defines the social determinants of health as "the conditions in which people are born, grow, live, work and age. These circumstances are shaped by the distribution of money, power and resources at global, national and local levels."¹ Social determinants of health lead to health inequities which results in the unjust and unnecessary differences in the health status and health indicators of individuals.¹ The difference in socioeconomic classes originate from people having different levels of education, income or occupation.² Those who are in the lowest socioeconomic classes have high levels of ill-health, poor health indicators and also premature mortality.³ In 2015 the global life expectancy was 71.4 years (73.8 years for females and 69.1 years for males). The life expectancy varied by WHO region, with the WHO European Region having a life expectancy of 76.8 years whilst that of the WHO African region was 60 years.³ Apart from the variations in life expectancy and mortality rates between countries, disparities are also noted between different socioeconomic classes in the same country. In a study conducted by Mackenbach *et al.* comparing mortality rates between 22 European countries, it was noted that the social inequalities in mortality rates were smaller in Southern Mediterranean countries when compared to the inequalities in central and eastern Europe.⁴

Globally health researchers have been trying to study and analyse the disparities in health outcomes between socioeconomic groups and their causes. However, it is very

challenging to highlight these differences to policy makers with a view to attempt to tackle and reduce these inequities and inequalities.⁵ The WHO's Commission on the Social Determinants of Health, recommends three ways by which health equity can be tackled and improved:

- equitable distribution of resources, power and money;
- measurement and evaluation of the impact of policies on inequity;
- taking action on health equity.⁶

THE MALTESE SCENARIO

In Malta there are various social benefits and social welfare services in place to try to bridge and minimise the gap between different socioeconomic classes and to reduce the impact of poverty. The 1970s saw the introduction of children's allowances, a national minimum wage and the introduction of two-thirds pension scheme. Also, in 1979 free hospitalisation was introduced as the first step towards the development of the National Health Service.⁷ Despite a generous welfare state, social inequalities still exist and according to the Statistics and Living Conditions survey carried out by the National Statistics office, the monetary at-risk-of-poverty rate stood at 16.3% or 68,658 individuals in 2015.⁸

Differences in socioeconomic conditions have an impact on health and longevity.⁹ A number of indicators can be used to monitor the effect of socioeconomic factors on health. Educational level, income and ethnicity are good indicators to study the impact of the socioeconomic status on health.

[IN MALTA] ... LITTLE IS KNOWN ABOUT THE EFFECT THAT HEALTH PROMOTION STRATEGIES HAVE ON DIFFERENT SOCIOECONOMIC CLASSES. IF HEALTH PROMOTION MESSAGES ARE MORE EFFECTIVE ON PEOPLE COMING FROM HIGHER SOCIOECONOMIC CLASSES ... THEY MIGHT BE INCREASING THE SOCIOECONOMIC GAP AND HEALTH INEQUITIES

Malta has seen a steady increase in life expectancy since the 1950s with rates comparable to the EU-15. However, disparities in life expectancy by educational level exist (Figure 1) with men having the lowest educational levels experiencing a life expectancy four and a half years less than those in the highest educational groups. Disparities between life expectancy in women is also present but to a lesser extent (1.7 years between those with the lowest and those with the highest educational level).¹⁰

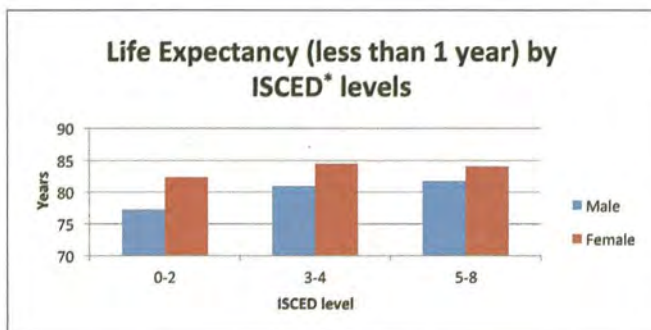


Figure 1. Life expectancy (less than 1 year) in 2011 by International Standard Classification of Education level.¹⁰

*1 ISCED: International Standard Classification of Education: Levels 0-2: from no education to secondary level education; 3-4: upper secondary and post-secondary non-tertiary; 5-8: tertiary level and above.

Analysis of cause-specific mortality may provide valuable insights on the source of health gaps observed between different socioeconomic groups. Regional analysis is sometimes used as a proxy for socioeconomic variables in the absence of more accurate indicators; however, regional differences may be the result of multiple factors and not only those related to socioeconomic classes. Figure 2 illustrates the age-standardised mortality rate due to circulatory diseases in Malta by region. The Western region, which is considered quite affluent,¹¹ has the lowest age-standardised mortality rate for males. On the other hand the Western region has the highest mortality rate from breast cancer in females (Figure 3). Breast cancer incidence is known to increase with increasing affluence and socioeconomic status.¹²

The inverse relationship between socioeconomic status and engaging in unhealthy behaviours such as unhealthy nutrition, lack of physical activity and smoking is well documented in literature.¹⁴ This high prevalence of unhealthy behaviours in individuals of lower socioeconomic status contributes further to inequalities in health.¹⁵ Results from the European Health Interview Survey (EHIS) carried out by the Directorate for Health Information and Research in 2014 highlight this inverse relationship; people with lower levels of education especially those of ISCED levels 0 to 2 have a higher prevalence of being overweight and obese, not engaging in any physical activity and smoking (Figures 4-6).¹⁰

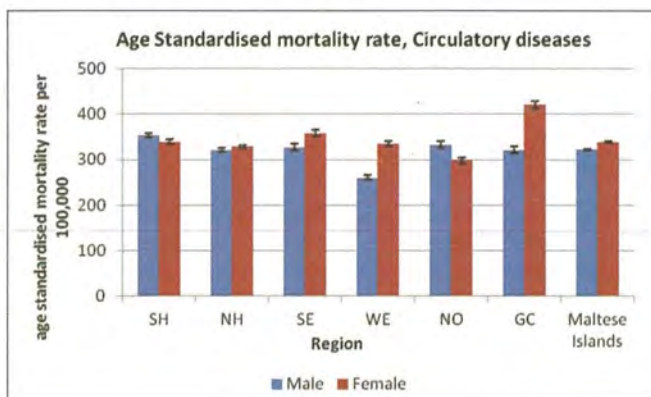


Figure 2. Standardised mortality rate 2014 secondary to circulatory disease by region.¹³ Regions: SH: Southern harbour district; NH: Northern harbour district; SE: South Eastern district; WE: Western district; NO: Northern district; GC: Gozo.

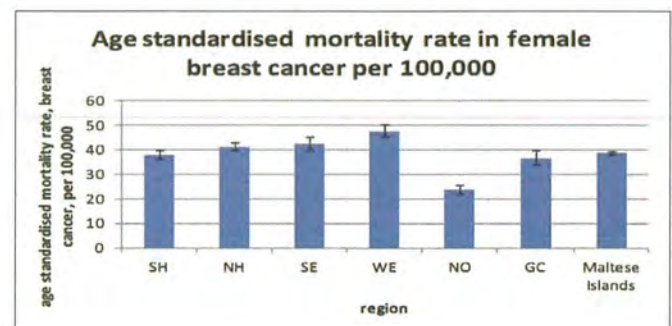


Figure 3. Age standardised mortality rate 2014 secondary to breast cancer by region.¹³

... THE WESTERN REGION [IN MALTA] HAS THE HIGHEST MORTALITY RATE FROM BREAST CANCER IN FEMALES

The way an individual perceives his or her own health status is also affected by socioeconomic determinants. In Malta and the EU, individuals with higher levels of education and higher income have a better perception of their health status (good or very good) (Figure 7). The perception of having a poor health may be related to the fact that people with lower levels of education report having more limitations in performing activities of daily living and also tend to suffer more from chronic diseases like coronary heart disease, hypertension, chronic depression and diabetes (Figure 8-9).

There is also an income gradient in relation to unmet health needs with those having lower incomes reporting a higher level of unmet health needs secondary to perceiving healthcare services as being too expensive, inaccessible or having long waiting times (Figure 10).¹⁰

DISCUSSION AND CONCLUSION

Over recent years many countries have improved the health status of their population but reducing the gap in health inequalities remains a challenge.² As observed in the figures above, locally there is a gradient in the socioeconomic effect on health. As documented in the Marmot report¹⁶ reducing health inequalities due to socioeconomic factors needs to focus on reducing the 'steepness of the social gradient on health' with increased intensity for the most disadvantaged groups in society. The Marmot report also states that reducing health

inequalities needs concerted effort at different domains such as education, employment and health and targeted approaches at different stages of a person's life.¹⁶

At both EU and national level it is important that all policies which are developed factor in social determinants and their impact on health. In Malta the National Strategic Policy for Poverty Reduction and Social Inclusion 2014-2024 was launched in December 2014.¹⁷ The mission statement of this policy is "to provide a policy framework that promotes the well-being and improves the quality of life for all, particularly for persons at risk of poverty or social exclusion, based on the values of solidarity, equality, dignity and respect for fundamental human rights and social justice". This policy acknowledges that everyone can be at risk of poverty and social exclusion but focuses more on the most vulnerable groups in the Maltese population: children, elderly, unemployed and working poor. The actions and objectives described in this strategy are aimed at preventing poverty and

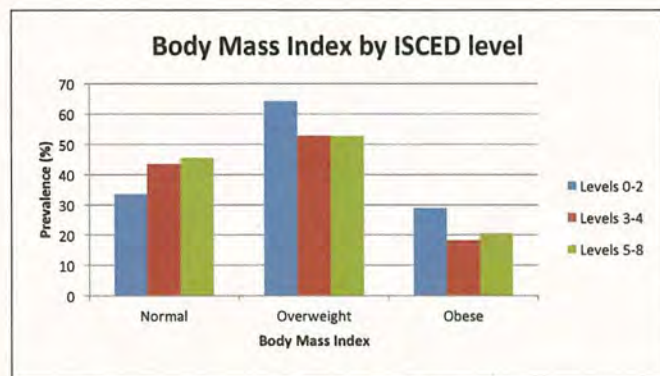


Figure 4. Body Mass Index by educational attainment (ISCED level).¹⁰

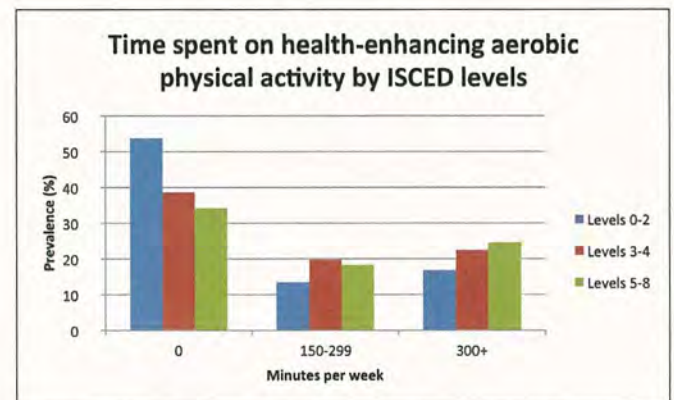


Figure 5. Time spent on health-enhancing aerobic physical activity by educational attainment (ISCED levels).¹⁰

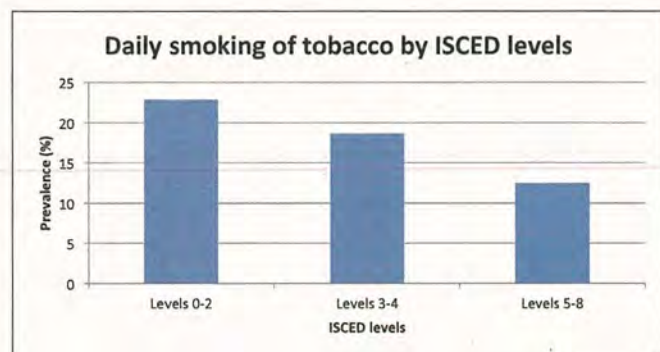


Figure 6. Daily smoking of tobacco by educational attainment (ISCED levels).¹⁰

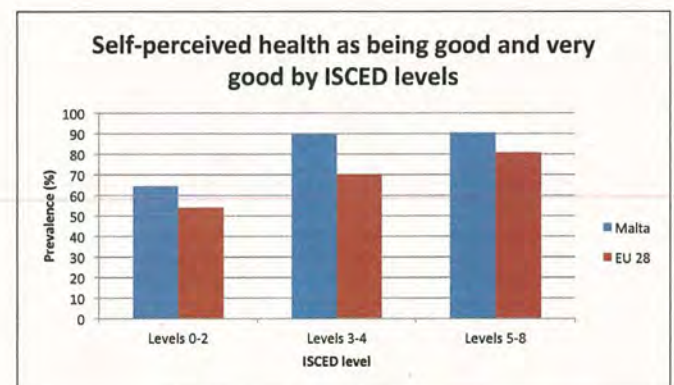


Figure 7. Self-perceived health as being good or very good by educational attainment (ISCED levels).¹⁰

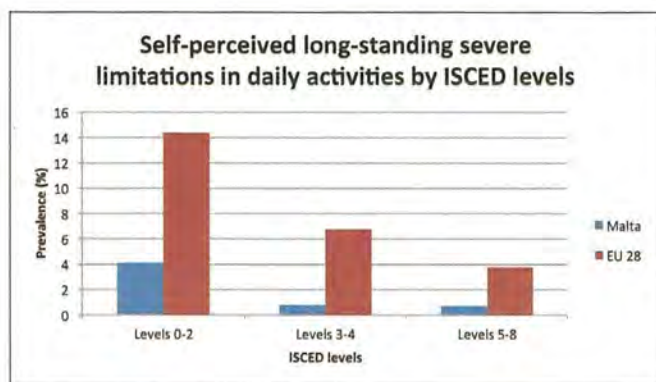


Figure 8. Self-perceived long-standing severe limitations in daily activities by educational attainment (ISCED levels).¹⁰

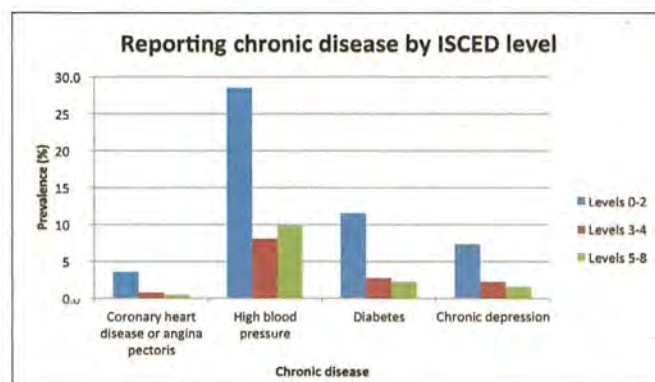


Figure 9. Maltese individuals reporting having a chronic condition by educational attainment (ISCED levels).¹⁰

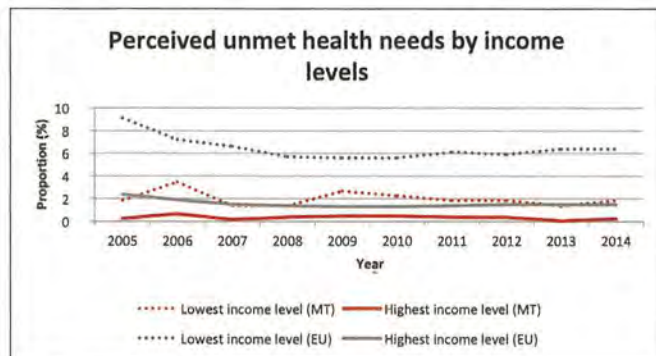


Figure 10. Perceived unmet health needs by income levels.¹⁰

social exclusion and improving the socioeconomic status of everyone especially the vulnerable groups. The actions described the strategy also explore different ways of ensuring equal access to quality healthcare, strengthening primary health care and mental health services and reducing unmet health needs.¹⁷

There is a gap in local literature on the mechanisms involved in the relationships between socioeconomic status, unhealthy behaviours and poor health outcomes.¹⁴ Little is known about the effect that health promotion strategies have on different socioeconomic classes. If health promotion messages are more effective on people coming from higher socioeconomic classes and less effective on those coming from lower socioeconomic classes, they might be increasing the socioeconomic gap and health inequities. The reason for this may be that the health literacy in individuals with high socioeconomic status is higher than that of individuals having a low socioeconomic class.¹⁵

The results of the Health Literacy Survey commissioned by the Office of the Commissioner of Mental Health in 2014 concluded that 48.9% persons with no or primary level of education had poor health literacy. The survey also found that low levels of health literacy were associated with low levels of self-perceived health.¹⁸

The need for further local research and monitoring of the socioeconomic effects on health is needed to highlight the impact that inequalities have on health outcome and to promote a more holistic approach to public health.

Reducing health inequities is an ethical and socially just imperative.¹⁶

REFERENCES


- World Health Organisation. Social determinants of Health [Internet]. [cited 2016 Nov 10]. Available from: http://www.who.int/social_determinants/sdh_definition/en/
- Mackenbach JP, Karanikolos M, Mckee M. The unequal health of Europeans : successes and failures of policies. *Lancet* [Internet]. Elsevier Ltd; 2013;381(9872):1125-34. Available from: [http://dx.doi.org/10.1016/S0140-6736\(12\)62082-0](http://dx.doi.org/10.1016/S0140-6736(12)62082-0)
- Commission on Social Determinants of Health, World Health Organisation. Closing the gap in a generation. 2008.
- Mackenbach JP, Roskam A, Menvielle G, Kunst A. Socioeconomic Inequalities in Health in 22 European Countries. *N Engl J Med*. 2008;358(23).
- The Lancet Global Health. Bridging the global health gap. *Lancet Glob Heal* [Internet]. The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY license; 2016;4(9):e579. Available from: [http://dx.doi.org/10.1016/S2214-109X\(16\)30190-5](http://dx.doi.org/10.1016/S2214-109X(16)30190-5)
- Khanal P, Bhattarai N. Health beyond health to bridge the global health gap. *Lancet Glob Heal* [Internet]. The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY license; 2016;4(11):e792. Available from: [http://dx.doi.org/10.1016/S2214-109X\(16\)30256-X](http://dx.doi.org/10.1016/S2214-109X(16)30256-X)
- Camilleri R. A Demographic and Socio-Economic Profile of Ageing in Malta. International Institute on Ageing (United Nations - Malta); 1993.
- National Statistics Office. Statistics on Income and Living Conditions 2015: Saliient Indicators. 2016;1-9.
- European Observatory on the Social Situation. Health Status and Living Conditions in an Enlarged Europe. 2005.
- European Commission. Eurostat [Internet]. 2016 [cited 2016 Jan 2]. Available from: <http://ec.europa.eu/eurostat/data/database>
- National Statistics Office. Statistics on Income and Living Conditions 2010: National Statistics Office 2012 https://nso.gov.mt/en/publicatons/Publications_by_Unit/Documents/CI_Living_Conditions_and_Culture_Statistics/SILC_2010.pdf.
- Robert S, Strombom I, Trentham-Dietz A, Hampton J, McElroy J, Newcomb P, et al. Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. *Epidemiology*. 2004;15(4):442-50.
- Directorate for Health Information and Research. Mortality Register. 2016.
- Pampel F, Kreuger P, Denney J. Socioeconomic Disparities in Health Behaviors. *Annu Rev Sociol*. 2011;(36):349-70.
- Lenthe FJ Van, Bourdeaudhuij I De, Klepp K, Lien N, Moore L, Faggiano E, et al. Preventing socioeconomic inequalities in health behaviour in TEENAGE. 2009;10:1-10.
- The Marmot Review Team. Fair society, healthy lives: strategic review of health inequalities in England post-2010. London: Marmot Review Team; 2010. 009;10:1-10.
- Ministry for the Family and Social Solidarity. National Strategic Policy for Poverty Reduction and for social inclusion 2014-2024. Ministry for the Family and Social Solidarity <http://mfss.gov.mt/en/Documents/Poverty%20Strategy%2014%20English%20Version.pdf>
- Office of the Commissioner for Mental Health. Health Literacy Survey, Malta 2014. Compiled by the National Statistics Office on behalf of the Office of the Commissioner for Mental Health.

NEW SAFETY INFORMATION ON AZITHROMYCIN

In the last few years the scientific community was debating the safety of the widely used macrolide antibiotic, azithromycin, which is commonly prescribed for respiratory and urinary tract infections.

Previously published observational studies examined the risk of cardiovascular outcomes with azithromycin use, but these studies had conflicting results. The first such study to be published, a cohort study using U.S. Medicaid data, found an increased risk of cardiovascular death with azithromycin use. This led the Food and Drug Association to issue a warning on the safety of azithromycin use, although the European Medicines Agency did not take a position on this issue. Subsequent studies, both in the U.S. and in Europe did not always observe a risk of cardiovascular adverse events. This was likely due to several factors. Some studies investigated the link between cardiovascular death and azithromycin use. However, cardiovascular death can be considered a rather ambiguous outcome given that the concern with azithromycin use should be ventricular arrhythmia specifically, based on the effect of macrolides on QT-interval prolongation. Cardiovascular death may be due to conditions unrelated to ventricular arrhythmia. It is therefore possible that the cardiovascular impact of azithromycin is over-estimated by using this general clinical outcome. Another important factor leading to variation among the published studies is the diversity in the underlying study populations. For example, a study conducted among persons with a lower socioeconomic status such as Medicaid beneficiaries may show a comparatively higher cardiovascular risk than a European population.

In order to extensively investigate the cardiovascular risk of azithromycin in a European population, a recently published study¹ investigated the risk of ventricular arrhythmia with azithromycin use in five European countries, i.e. Denmark, Italy, Germany, the Netherlands

and UK, using a common methodology applied to seven healthcare databases. This allowed the researchers to reach a very large study sample of over 14 million new antibiotic users. The results of this study, published last April in the *Canadian Medical Journal* indicate a higher risk of ventricular arrhythmia in azithromycin users when compared to non-users of antibiotics, but no excess risk compared to the use of amoxicillin, a widely used antibiotic not considered to be associated with any cardiovascular events. These findings suggest that the risk of ventricular arrhythmia with azithromycin use is likely to be mainly due to the poor state of health from the underlying infection rather than the drug itself. The primary analyses from the single databases were robustly tested through meta-analysis of the pooled risk estimates obtained from all the databases together, confirming the findings of the primary analysis. 

The referenced article is freely available from the Canadian Medical Journal website, i.e. <http://www.cmaj.ca/content/189/15/E560.full.pdf+html>.

The principal investigator of the study, Prof. Gianluca Trifiro', leads a pharmacoepidemiology research team based in Messina. Dr Janet Sultana was one of the co-investigators and is a Maltese joint post-doctoral researcher at the University of Messina and the Erasmus Medical Centre, working in his team based in Sicily. She can be contacted on jaysultana@gmail.com.

REFERENCE

1. Trifirò G, de Ridder M, Sultana J, et al. Use of azithromycin and risk of ventricular arrhythmia. *CMAJ* 2017;189(15):E560-E568.

HEPATITIS

Hepatitis can be defined in simple terms as an inflammation of the liver. There are various causes of hepatitis; the most common are viral infections (Hepatitis A, B and C) and Alcoholic Hepatitis. While these causes all result in liver damage, it is important to note that these diseases are distinct from each other and have different symptoms, treatments and risk factors.

Hepatitis A is caused by the Hepatitis A virus (HAV). This virus is transmitted mainly through food and water contaminated with the faeces of an infected person. Poor sanitation and lack of clean water are the two main risk factors for Hepatitis A. Hepatitis A causes acute liver failure and generally isn't fatal.

Hepatitis B is caused by the Hepatitis B virus and is spread by contact with blood or other bodily fluids of infected persons. Hepatitis B can cause both chronic and acute liver failure and can be rapidly fatal.

Hepatitis C is caused by the Hepatitis C virus. This particular virus is blood-borne, those most at risk of developing Hepatitis



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C are IV drug users who partake in the sharing of needles. Hepatitis C can cause both acute and chronic liver failure.

Alcoholic Hepatitis is caused by sustained excessive alcohol intake over a period of years. Symptoms include jaundice and abdominal distention due to fluid build-up. Alcoholic Hepatitis usually leads to chronic liver failure. Liver Cirrhosis is also commonly observed in patients suffering from Alcoholic Hepatitis.

There are vaccines available that can easily prevent Hepatitis A and B. There is no vaccine available for Hepatitis C and Alcoholic Hepatitis but taking simple precautions such as limiting alcohol intake and safe handling of needles can help prevent these diseases.

Every year WHO organizes World Hepatitis Day on the 28 July in order to increase awareness about the disease. 

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AN UPDATE ON PRIONS AND PRION-LIKE DISORDERS

ABSTRACT

Prions are infectious agents composed of protein material. Prions fold in multiple ways, at least one of which is transmissible to other prions; transmission between species leads to prion diseases, such as the more commonly known “mad cow disease”. Similar to prion diseases, other neurodegenerative diseases are also associated with the accumulation of self-templating amyloid forms of specific proteins. For example, β -amyloid and tau misfold in Alzheimer’s disease, α -synuclein in Parkinson’s disease, huntingtin in Huntington’s disease, and TDP-43 and FUS aggregate in neurons in ALS. In this review, we will discuss why these diseases are often dubbed prion-like.

PRIONS AND PRION DISEASES?

Prions are pure proteinaceous infectious particles. They reproduce by recruiting the normal cellular prion protein (PrP^C), which is a membrane glycoprotein, and stimulating its conversion to the disease-causing (scrapie) isoform (PrP^{Sc}). PrP^C and PrP^{Sc} are identical in composition but differ in their 3D structures; PrP^C is rich in α -helices and has little β -sheet whereas PrP^{Sc} is less rich in α -helices and has much more β -sheet. In this cross-beta fibrous structure, termed amyloid, the strands of the β -sheets align orthogonal to the fibre axis. Such fibres elongate at both ends, and the fibre ends capture and convert the natively folded proteins to the cross-beta form. Overall, this structural transition from α -helices to β -sheet in PrP, known as permissive templating, is the fundamental event that underlies prion diseases.¹

Prion diseases are a collection of fatal neurodegenerative disorders that afflict mammals, including Creutzfeldt-Jakob disease (CJD), Fatal Familial Insomnia (FFI), Gertsmann-Straussler-Scheinker syndrome (GSS), Kuru and Variably Protease-Sensitive Prionopathy (VPSP), in humans.

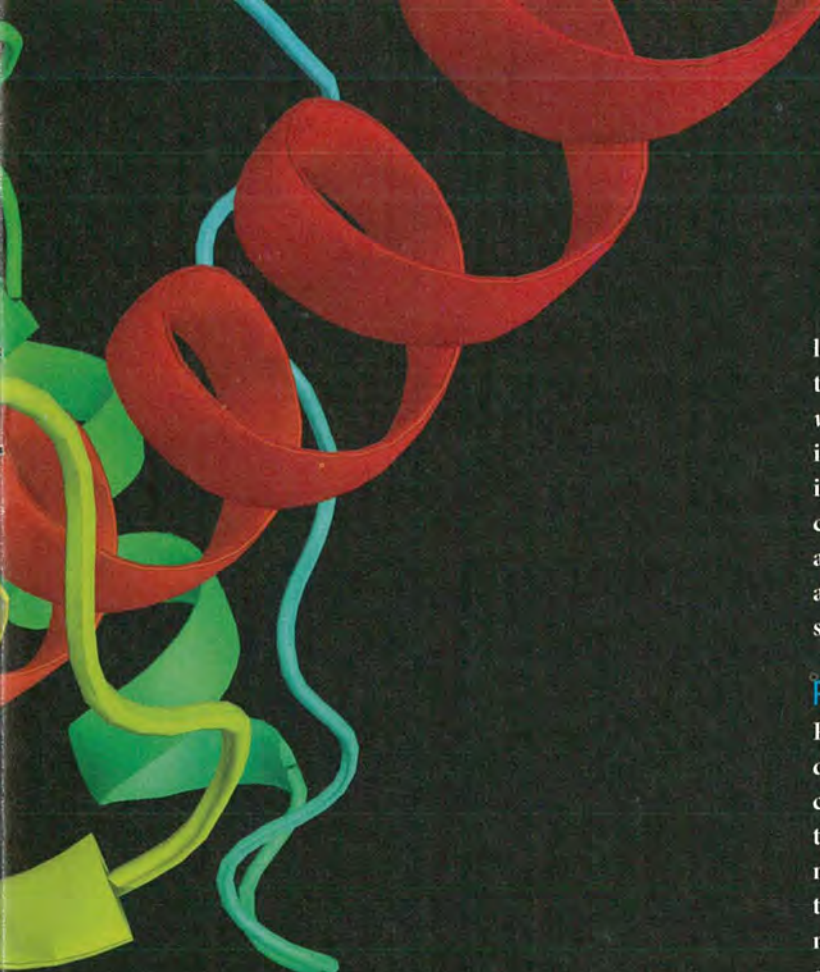
Transmission between individuals, and sometimes even between species, is possible due to the stability of the cross-beta prion form, which is resistant to denaturation, detergents, and proteases.² For example, in Europe, industrial cannibalism has been responsible for “mad cow disease”. In general, it is the presence of the PrP amyloid plaques that is diagnostic of these transmissible spongiform encephalopathies.

PRION-LIKE DISORDERS

Interestingly, this ability to access self-templating amyloid forms is not unique to prion proteins. Several neurodegenerative diseases are also associated with the accumulation of self-templating amyloid forms of specific proteins, e.g. β -amyloid (A β) and tau misfold in Alzheimer’s disease (AD), α -synuclein misfolds in Parkinson’s disease (PD), and huntingtin misfolds in Huntington’s disease (HD). Several research studies support the possibility that these disorders and their respective amyloid forms are more transmissible and prion-like than previously suspected.³ Such findings have therapeutic implications and blur the distinctions between amyloid and prion, and between transmissibility and infectivity.

ALZHEIMER’S DISEASE

AD is the most common neurodegenerative disorder, affecting approximately 35 million people worldwide. In AD, the defining pathological lesions are the neuritic plaques



composed of A β peptides. A β is a cleavage peptide of the amyloid precursor protein (APP). It varies in size from 39 to 43 amino acids, but the main species observed in the plaques are A β 40 and A β 42. A β 40 is more common, whereas A β 42 is more fibrillogenic and is therefore more associated with disease states.⁴ Similar to a prion protein, pure A β 40 forms fibres with different molecular structures, which are toxic to neurons in culture. Likewise, A β amyloid forms accumulate in the extracellular space, and therefore transmissibility becomes a concern. Indeed, when brain extracts from patients with AD were introduced into the brains of transgenic mice generating human APP, the material induced plaque formation and deposition of A β . In contrast, introducing brain extracts from age-matched patients without AD showed less A β accumulation.⁵ Moreover, coherent with the property of permissive templating, plaques did not appear in mice that did not produce human A β . It is thus probable that transmission from extract to host brain occurs through pure protein templating.

In AD, A β is not the only protein that can access an amyloid form. Tau is a protein that binds to and stabilises microtubules, thus enabling intracellular transport. Six tau isoforms are expressed in the human brain. During AD, tau dissociates from microtubules and forms amyloid accumulations throughout the cell.⁶ Specifically, filamentous inclusions, made up of all 6 isoforms, form in a stereotypical manner, underlying the “Braak stages” of tau pathology. Tau pathology begins in discrete regions but ultimately involves

larger areas of the brain. Such an intercellular transfer of tau aggregates has been described in both *in vitro*⁷ and *in vivo*⁸ experiments. In general, tau is considered to be an intracellular protein. However, tau aggregates are detected in the extracellular space, and tau peptide is observed in the cerebrospinal fluid of patients. Frost *et al.*⁷ hypothesised and showed that extracellular tau aggregates can transmit a misfolded state from the outside to the inside of a cell, similar to prions.

PARKINSON'S DISEASE

PD is the most common neurodegenerative movement disorder, afflicting people over 65 years of age. It is caused by selective damage to dopaminergic neurons in the substantia nigra.⁹ While PD is sporadic, a few gene mutations have been associated with familial forms of the disease; these include gene multiplications and point mutations in the SNCA gene, which encodes α -synuclein. α -synuclein is a small (140 a/a) presynaptic protein that binds lipids through its amino-terminal repeat region. It is believed to play a role in the assembly of the protein complexes required for chemical neurotransmission. In PD, the signature lesions are cytoplasmic aggregates in dopaminergic neurons known as Lewy bodies (LBs) and Lewy neurites (LNs), consisting of amyloid forms of α -synuclein. Curiously, α -synuclein pathology also hints at a prion-like mechanism of propagation through the brains of patients with PD; the propagation of LB and LN pathology has been described in both *in vitro*¹⁰ and *in vivo*¹¹ experiments.

Steiner *et al.*¹⁰ showed that the propagation of the amyloid forms of α -synuclein requires two steps. Step 1 is the exit of α -synuclein from the dying neuron; upon cell death, degenerating neurons release α -synuclein fibres. α -synuclein aggregates are then incorporated into vesicles and secreted from neurons via exocytosis. Step 2 is the entry of α -synuclein into the recipient cell. It is however still unclear how α -synuclein escapes a membrane-bound vesicle to form cytoplasmic aggregates. In cell culture, it was discovered that inhibiting lysosomal function results in the deposition of α -synuclein.¹² Interestingly, mutations in PARK9, a lysosomal transmembrane ATPase, are connected with familial Parkinsonism. In addition, overexpression of PARK9 was found to counter α -synuclein toxicity.¹³ Therefore, a decline in lysosomal function with age might contribute to α -synuclein pathogenesis by facilitating transmission and reducing clearance of α -synuclein in the lysosome.¹⁴ For this reason, restoring lysosomal function could be one of several strategies for curing PD.



HUNTINGTON'S DISEASE

HD is an autosomal dominant neurodegenerative disorder. It is characterised by a loss of striatal neurons in the basal ganglia; however, pathology is observed in other areas of the brain as well. HD is caused by a trinucleotide (CAG) repeat expansion in the huntingtin gene.¹⁵ Specifically, it is the expansion of a CAG repeat in exon 1 of the huntingtin gene above a threshold of 35 to 40 CAG repeats that causes the disease. In turn, this mutation encodes an expanded polyglutamine (polyQ) tract, which makes the protein prone to aggregate and to form intraneuronal inclusion bodies.¹⁶ It has been found that the longer the polyQ tract, the faster the aggregation, and the earlier the onset. In the *Drosophila melanogaster* brain, Pearce *et al.*¹⁷ observed prion-like transmission of neuronal huntingtin aggregates to phagocytic glia.

AMYOTROPHIC LATERAL SCLEROSIS


Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is a neurodegenerative disease that devastates the upper and lower motor neurons. ALS starts in a discrete location but progresses to involve neighbouring regions of the motor system. Recently, mutations in two RNA binding proteins, TDP-43 and FUS, were identified in patients with familial ALS. It was found that in ALS both TDP-43 and FUS form aggregates in neurons. Furthermore, evidence indicates that both proteins contain prion-related modular domains. Indeed, both have domains highly enriched in glutamine (Q) and asparagine (N) residues that meet the criteria for prion-related domains. Also, both form aggregates, and both

are cross-seeded into polyQ inclusions, mediated by the Q/N rich region, similar to other prion-related domain containing proteins.¹⁸

CONCLUSION

Even if most neurodegenerative diseases don't spread from individual to individual like true prion diseases do, the possibility that they may spread from cell to cell in an analogous way has important implications for potential therapies, especially in view of stem-cell and neuronal-graft based therapies. For example, because PrP acts as a receptor for toxic A β oligomers, grafted neurons might be useful for the treatment of AD; grafted neurons would resist A β oligomer invasion.¹⁹ Likewise, depleting tau or α -synuclein from grafted neurons might prove advantageous in tauopathies and PD, respectively. Indeed, depletion of PrP or tau, even after the onset of the disease, was shown to be an efficient treatment of prion and prion-like diseases in mouse models.²

Translational research on prions is fast-paced. On the diagnostic side is a blood-test to diagnose Variant Creutzfeldt-Jakob Disease (vCJD).²⁰ Indeed, the test has the potential to detect presymptomatic patients. Given the fact that there is evidence of silent carriers, such a diagnostic test will surely limit the risk of vCJD transmission through blood transfusion. On the therapeutic side, multiple pathways are being followed, involving small molecule drugs, antibodies, gene silencing, vaccines and stem cell therapy.

In view of all this, and as the current studies and existing knowledge of prion pathogenesis are augmented, there is optimism that a much better understanding of the pathogenic pathways will lead to more rational therapeutics. 

REFERENCES

1. Prusiner SB. Shattuck Lecture - Neurodegenerative Diseases and Prions. *The New England Journal of Medicine* 2001; 344(20):1516-26.
2. Cushman M, Johnson BS, King OD, Gitler AD, Shorter J. Prion-Like Disorders: Blurring the Divide between Transmissibility and Infectivity. *Journal of Cell Science* 2010; 123(Pt 8):1191-201.
3. Frost B, Diamond MI. Prion-Like Mechanisms in Neurodegenerative Diseases. *Nature Reviews Neuroscience* 2010; 11(3):155-9.
4. Duyckaerts C, Delatour B, Potier MC. Classification and Basic Pathology of Alzheimer Disease. *Acta Neuropathologica* 2009; 118(1):5-36.
5. Meyer-Luehmann M, Coomaraswamy J, Bolmont T, et al. Exogenous Induction of Cerebral Beta-Amyloidogenesis is Governed by Agent and Host. *Science* 2006; 313(5794):1781-4.
6. Forman MS, Trojanowski JQ, Lee VM. Neurodegenerative Diseases: a Decade of Discoveries Paves the Way for Therapeutic Breakthroughs. *Nature Medicine* 2004;10(10):1055-63.
7. Frost B, Jacks RL, Diamond MI. Propagation of Tau Misfolding from the Outside to the Inside of a Cell. *The Journal of Biological Chemistry* 2009; 284(19):12845-52.
8. Clavaguera F, Bolmont T, Crowther RA, et al. Transmission and Spreading of Tauopathy in Transgenic Mouse Brain. *Nature Cell Biology* 2009; 11(7):909-13.
9. Skovronsky DM, Lee VM, Trojanowski JQ. Neurodegenerative Diseases: New Concepts of Pathogenesis and their Therapeutic Implications. *Annual Review of Pathology* 2006; 1:151-70.
10. Steiner JA, Angot E, Brundin P. A Deadly Spread: Cellular Mechanisms of Alpha-Synuclein Transfer. *Cell Death and Differentiation* 2011; 18(9):1425-33.
11. Mougnot AL, Bencsik A, Nicot S, et al. Transmission of Prion Strains in a Transgenic Mouse Model Overexpressing Human A53T Mutated Alpha-Synuclein. *Journal of Neuropathology and Experimental Neurology* 2011; 70(5):377-85.
12. Desplats P, Lee HJ, Bae EJ, et al. Inclusion Formation and Neuronal Cell Death through Neuron-to-Neuron Transmission of Alpha-Synuclein. *PNAS* 2009; 106(31):13010-5.
13. Gitler AD, Chesi A, Geddie ML, et al. Alpha-Synuclein is Part of a Diverse and Highly Conserved Interaction Network That Includes PARK9 and Manganese Toxicity. *Nature Genetics* 2009; 41(3):308-15.
14. Cuervo AM, Stefanis L, Fredenburg R, et al. Impaired Degradation of Mutant Alpha-Synuclein by Chaperone-Mediated Autophagy. *Science* 2004; 305(5688):1292-5.
15. Scherzinger E, Lurz R, Turmaine M, et al. Huntingtin-Encoded Polyglutamine Expansions Form Amyloid-Like Protein Aggregates In Vitro and In Vivo. *Cell* 1997; 90(3):549-58.
16. Brundin P, Melki R, Kopito R. Prion-Like Transmission of Protein Aggregates in Neurodegenerative Diseases. *Nature Reviews Molecular Cell Biology* 2010; 11(4):301-7.
17. Pearce MM, Spartz EJ, Hong W, Luo L, Kopito RR. Prion-Like Transmission of Neuronal Huntingtin Aggregates to Phagocytic Glia in the *Drosophila* Brain. *Nature Communications* 2015; 6:6768.
18. Udan M, Baloh RH. Implications of the Prion-Related Q/N Domains in TDP-43 and FUS. *Prion* 2011; 5(1):1-5.
19. Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular Prion Protein Mediates Impairment of Synaptic Plasticity by Amyloid-Beta Oligomers. *Nature* 2009; 457(7233):1128-32.
20. Bougard D, Brandel JP, Belongrade M, et al. Detection of Prions in the Plasma of Presymptomatic and Symptomatic Patients with Variant Creutzfeldt-Jakob Disease. *Science Translational Medicine* 2016; 8(370):370ra182.



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YE OLDE APOTHECARY IN RABAT

THERE WAS A DAY AND AGE WHEN MEDICINES WERE NOT MASS PRODUCED, BUT HANDMADE TO DOCTOR'S ORDERS BY NONE OTHER THAN THE VILLAGE PHARMACIST. **MARIKA AZZOPARDI** REKINDLES SOME MEMORIES DURING A VISIT TO MALTA'S ONLY PHARMACY MUSEUM. SHE INTERVIEWS **MR MICHAEL BONNICI**.

The minute I step in, I am thrown back several decades to a time and place when as a child my mother took me with her to the local pharmacist. The scent of medical concoctions is the same, the lingering smell of pills and potions transports me back to a memory which no child of the 80s or later could relive.

This is the unique old pharmacy located within the building that houses the National Archives in Rabat. This may sound all too confusing and quite disjointed, so I should provide some explanation to the reader. The National Archives are found in Hospital Street in Rabat, Malta. The street name bears witness to the very same building wherein the archives are housed, the Santo Spirito Hospital. This hospital dates back to 1372 and ceased to serve as a hospital in the 1960s. As a stand-alone hospital, it enjoyed the luxury of having its own resident 'aromatorio' who managed the pharmacy housed within the building. And it is the self-same pharmacy I am visiting today.

To greet me is Mr Michael Bonnici, a former MP and Deputy Speaker of the House of Representatives. He is also a retired pharmacy technician who lived in a pharmacy practically all his life. 'My father owned the very old De Rohan Pharmacy of Ħaż-Żebbug which he bought in 1933 and which I bought from him. It was a "casa bottega" and so we grew up ensconced in the world of medicine. When I retired, I wanted

to donate some of my father's books to the National Archives. And that is how I chanced upon this old pharmacy.'

The small rooms were in a state of disrepair, although the original furniture was still in very good shape. 'I was enticed by the challenge of reviving this abandoned pharmacy and re-creating it to a semblance of its old self. It was intact although deprived of its original jars and accessories. My initiative set in a motion a process that has allowed for it to become what it is today.'

A tiny museum uniquely open by appointment, this pharmacy allows one the opportunity of travelling back in time. Because Mr Bonnici not only saw to it that the furniture got to be preserved and rehabilitated, but also continued to donate much of his own and of his father's antique pharmacy jars, bottles and equipment. He also embarked on an earnest and ongoing search through antique shops, auctions and flea markets with the purpose of re-stocking the pharmacy with any antique pharmaceutical item he would come across.

'This history of pharmacy in Malta is very long and intriguing. We were fortunate to receive much teaching from the Knights but also from religious orders such as the Franciscans who opened this hospital in the first place. And with the help of many curious items, I can show visitors how the pharmacist of old would go about dispensing medicine, as well as providing a service to the community and a supporting hand to the doctor in town.'

“

THIS HISTORY OF PHARMACY IN MALTA IS VERY LONG AND INTRIGUING. WE WERE FORTUNATE TO RECEIVE MUCH TEACHING FROM THE KNIGHTS BUT ALSO FROM RELIGIOUS ORDERS SUCH AS THE FRANCISCANS WHO OPENED THIS HOSPITAL IN THE FIRST PLACE.

Consider pills, or tablets as they were usually called. These did not come ready packed in plastic blister packs as they do today, nor were they mass produced in factories. Tablets were made by the pharmacist according to the doctor's prescription or according to his own knowledge of what would assist the patient. The pharmacist would measure and mix powders into a paste, roll it out and cut up to the correct size and weight of tablet with special tools. The final tablets would be finished off with a powder to avoid them from sticking together. Capsules also existed, and these were made out of digestible rice paper shaped like tiny flat round tubs with a base and a lid to them, in which the special mixture of powder was deposited and closed in.

There are the curios, such as a complete box full of injection vials belonging to a doctor in action during WWII. Or the dropper bottles made entirely of fine glass and incorporating a special minuscule groove that controls each and every drop. And of course, there are the medicine jars full of still fragrant oils such as eucalyptus. I learn that the medicine bottles come in different colours and details for a purpose. Dark brown and smooth glass bottles were



meant for natural oils or minerals which required darkness to remain effective. Blue and ridged bottles indicated a poisonous substance. Green bottles indicated corrosive substances.

And what about the old ledgers which belonged to Mr Bonnici Snr, full of hand-written and numbered prescriptions, all diligently documented on a daily basis to a total of 110,000 prescriptions in a lifetime ... there is so much more to take in, observe, ask questions about and Mr Bonnici is a fount of information, knowledge and memories to draw upon. So much so, that one single visit to this unique museum pharmacy is simply not enough. ✚



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ULTRASOUND OF THE INGUINAL CANAL

PART II

PIERRE VASSALLO

UNDESCENDED TESTES

During the embryological period, a testis that fails to reach its scrotal destination is referred to as an undescended testis. An undescended testis may lie anywhere along its path of migration, but is most commonly located in the inguinal canal. Statistically, 30% of premature male neonates have an undescended testis. At normal mature birth, the frequency falls to 2.7-5.9%, whereas at 1 year of age this is seen in 1.2-1.8% of cases. Normally, after 1 year of age, the testis will not descend any further. Ninety percent of undescended testes are associated with a patent processus vaginalis and 50% with an indirect inguinal hernia.

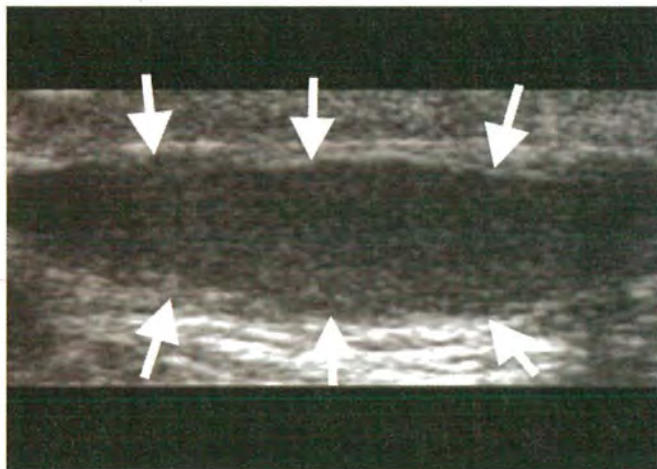


Figure 10. Ultrasound scan through the inguinal canal showing a flattened undescended testis (arrows).

Ultrasound is an excellent tool for rapidly locating an inguinal testis (Fig 10). For more proximal (intraabdominal) locations, computed tomography and magnetic resonance imaging are required. Ultrasound shows the size and texture as well as the vascularity of an inguinal testis; these features are important since there is an increased incidence of testicular cancer (2 to 8 times normal) and of testicular torsion in undescended testes.

A potential pitfall in young boys is the presence of a retractile testis. Retractable testes can be manually reduced to scrotal location whereas undescended testes cannot; this is readily established with ultrasound.

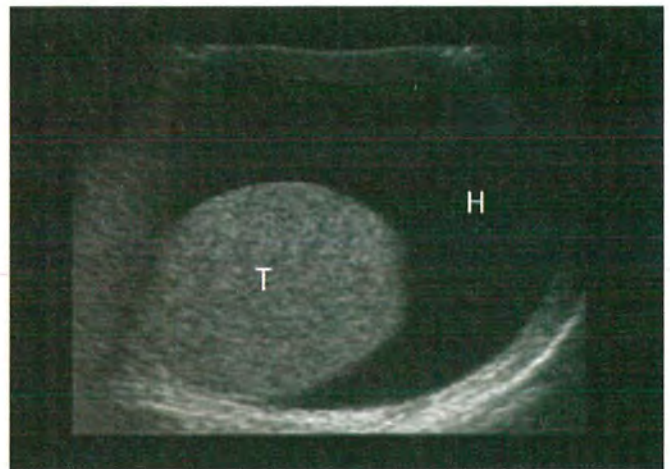


Figure 11. Ultrasound scan through the scrotum showing the testis (T) surrounded by a hydrocoele (H).

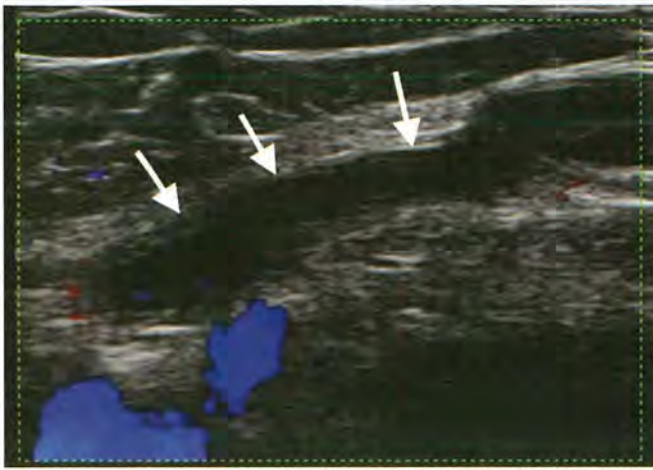


Figure 12. Ultrasound scan along the length of the inguinal canal showing a persistent canal of Nuck (arrows).

HYDROCOELES

Classically, a hydrocoele is a fluid collection contained within the tunica vaginalis that surrounds the testis (Fig 11). However, this may communicate with the peritoneal cavity through a patent processus vaginalis (Fig 12). Any segment of the processus vaginalis may persist and distend with fluid resulting in cysts located along the inguinal canal. Testicular hydrocoeles are most commonly seen in older men and are most likely the result of ascending infection through the vas deferens and are possibly related to prostatic enlargement. However, hydrocoeles are seen in association with testicular torsion and testicular neoplasms, conditions that are readily detected by ultrasound.

VARICOCELES

Varicoceles are distended (varicosed) testicular veins that are seen in the inguinal canal and scrotum. The cut-off diameter for detecting venous distention is 2-3mm. Any veins that are wider are considered varicoceles (Fig 13). Varicoceles are most commonly primary and are the result of incompetent testicular venous valves causing increased back pressure within the testicular veins from the intraabdominal veins. Secondary varicoceles occur because of intraabdominal venous obstruction or compression by a retroperitoneal neoplasm. A newly diagnosed varicocele should prompt imaging of the retroperitoneum to exclude this possibility.

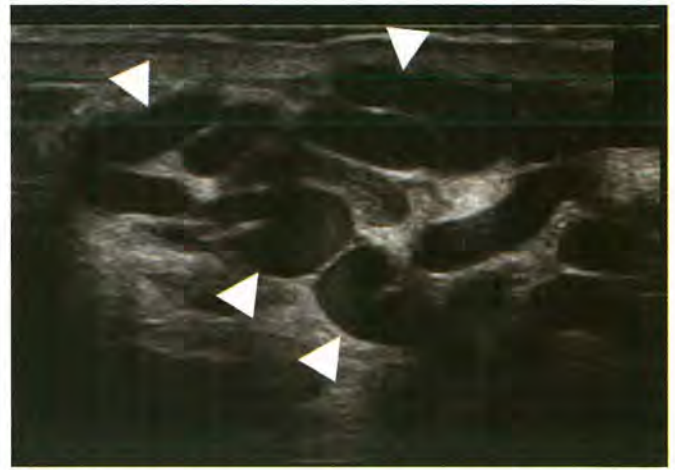


Figure 13. Ultrasound scan showing numerous distended veins (arrowheads) in the inguinal canal.

In women, the testicular vein equivalents are the veins of the round ligament; round ligament varices are also known to occur (Fig 14). These are most common during pregnancy and are more likely to present with acute pain than the male variety.

OTHER CONDITIONS OF THE INGUINAL CANAL

Corditis (inflammation of the vas deferens), endometreous deposits and benign tumours in the inguinal canal (lipomas, leiomyomas, lymphangiomas and cystadenomas) are uncommon conditions that are readily detected by ultrasound.

However, malignant lesions such as sarcomas and lymphoma are not uncommon and detection of a solid mass in the inguinal canal should prompt biopsy. This also holds true for suspicious regional lymphadenopathy. Enlarged (>1cm), rounded lymph nodes that do not demonstrate a central echogenic hilum require percutaneous biopsy (Fig 15). Flat elongated lymph nodes with wide central hila may be observed as they are usually reactive nodes secondary to inflammatory disease in the area of lymphatic drainage (Fig 16).

Many pathologic conditions can affect the inguinal canal. Ultrasound proves an invaluable tool for the detection and characterization of disease processes at this site. Knowledge of the ultrasound findings of these disease entities can lead to efficient and accurate management without the use of ionizing radiation or complex imaging modalities. ❄️

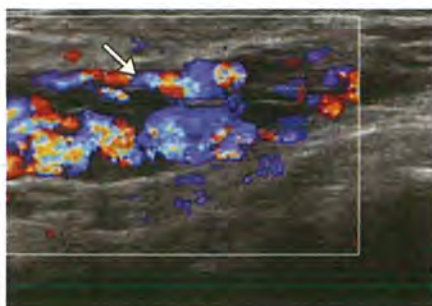


Figure 14. Doppler ultrasound scan showing a varicocele of the round ligament as numerous distended veins (arrow) in the inguinal canal in a woman, who was in her third trimester of pregnancy.



Figure 15. Ultrasound scan showing an enlarged rounded inguinal lymph node (arrows) with no central echogenic hilum; these features suggest malignant disease.

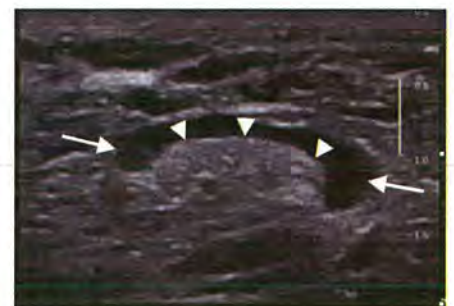


Figure 16. Ultrasound scan showing an enlarged flat/oval inguinal lymph node (arrows) with a wide central echogenic hilum (arrowheads), features most suggestive of an inflammatory/reactive process.





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