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thesynapse

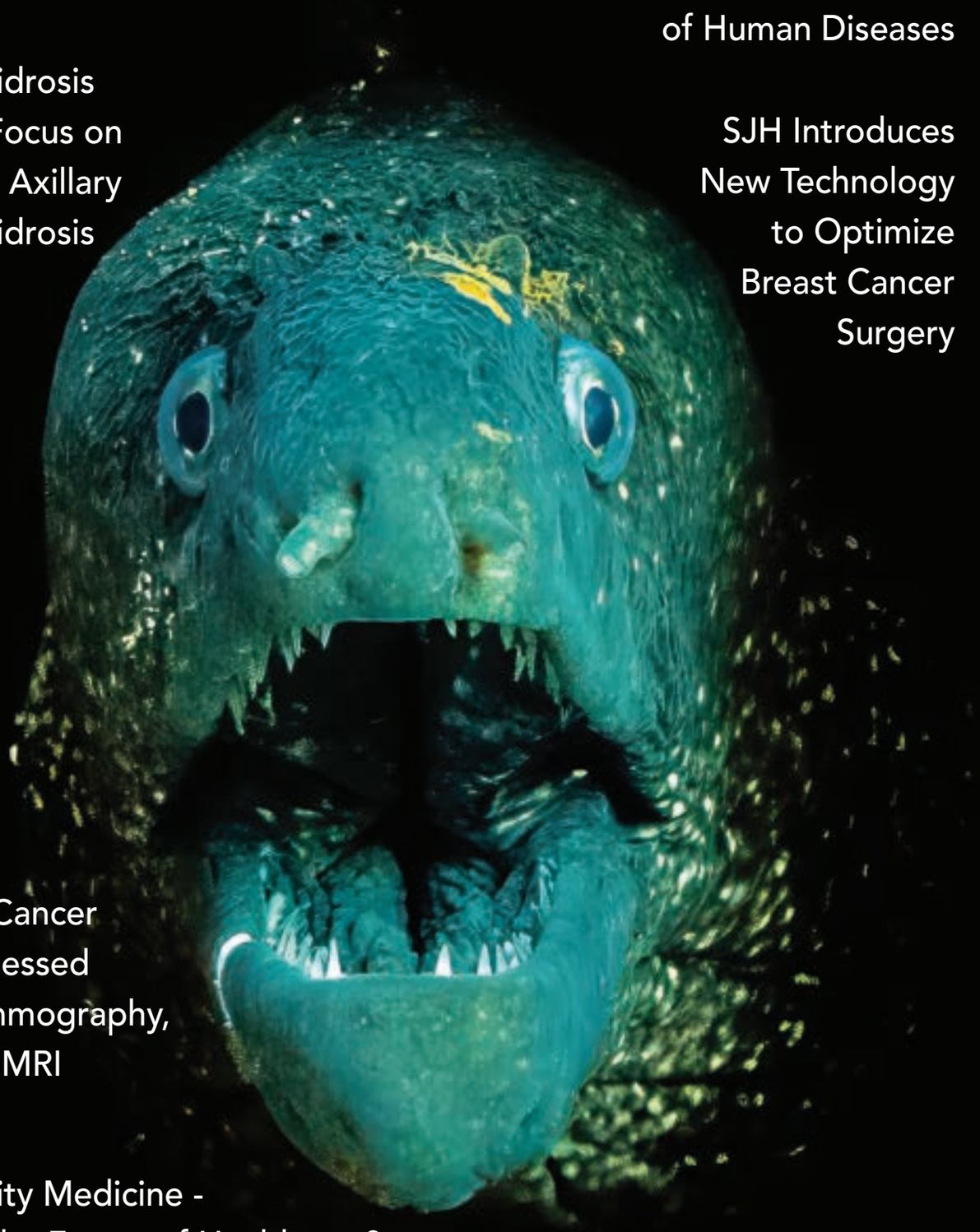
THE MEDICAL PROFESSIONALS' NETWORK

A Challenging Case of Tuberculosis

Translational Research of Human Diseases

Hyperhidrosis with a Focus on Primary Axillary Hyperhidrosis

SJH Introduces New Technology to Optimize Breast Cancer Surgery



Breast Cancer Risk assessed by Mammography, US and MRI

Longevity Medicine - Is This the Future of Healthcare?

ENTRESTO® (sacubitril/valsartan)

Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).

Indications: Adult heart failure: indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Paediatric heart failure: indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

Dosage & administration: General considerations: Entresto should not be co administered with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy. The valsartan contained within Entresto is more bioavailable than the valsartan in other marketed tablet formulations. If a dose is missed, the patient should take the next dose at the scheduled time. Adult heart failure: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. Paediatric heart failure: The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient. Entresto film-coated tablets are not suitable for children weighing less than 40 kg. Entresto granules are available for these patients. Elderly: The dose should be in line with renal function of the elderly patient. Renal impairment: No dose adjustment is required in patient with mild renal impairment. Hepatic impairment: No dose adjustment is required when administering Entresto to patients with mild hepatic impairment (Child Pugh A classification). Paediatric population: The safety and efficacy of Entresto in children aged below 1 year have not been established. Method of Administration: Oral use. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy.

Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co-administered with another ARB containing medicinal product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg for adult patients or ≥5th percentile SBP for the age of the paediatric patient. Patients with SBP below these values were not studied. Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg).

Blood pressure should be monitored routinely when initiating or during dose titration with sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended. Renal impairment: Patients with mild/moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Worsening renal function: Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non steroidal anti inflammatory agents (NSAIDs). Down titration should be considered in patients who develop a clinically significant decrease in renal function. Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l in adult patients and >5.3 mmol/l in paediatric patients. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It must not be re administered. Patients with a poor history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with New York Heart Association (NYHA) functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. Hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients. Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child Pugh C classification). Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered. Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially 'sodium free'.

Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co administered with another ARB. Use with caution when co-administering sacubitril/valsartan with statins or PDE5 inhibitors.No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartan is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Co-administration of sacubitril/valsartan and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co-administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of sacubitril/valsartan with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

Fertility, pregnancy and lactation: The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether sacubitril/valsartan is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of sacubitril/valsartan to the mother.

Undesirable effects: Very common (≥ 1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥ 1/100 to <1/10): Anaemia, hypokalaemia, hyperglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥ 1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema.

Packs sizes: Entresto 24 mg/26 mg - x28 tablets; Entresto 49 mg/51 mg - x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.

Legal classification: POM.

Marketing Authorisation Holder: Novartis Europharm Ltd. Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg

film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.

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NOVARTIS

Entresto® sacubitril/valsartan

GUEST EDITORIAL

DR JO ETIENNE ABELA
Minister for Active Ageing

Wanted – Nobel Prize Winners

The last quarter of each year is always busy. In Malta, we tend to be weighed down by discussions and debates revolving around the budget in October, and rightly so. October is also tied to awareness and preventive care with various laudable Pink October campaigns targeting breast cancer in women and testicular cancer in males. There is also the Movember movement which promotes health through a male lens focusing on prostate cancer awareness during November. November is also dedicated to raising awareness about pancreatic cancer.

October is the month which is associated with appreciation for older persons, indeed October 1st is the United Nations International Day dedicated to them. In October we also get to know the year's Nobel Prize laureates in the fields of peace, chemistry, physics, literature and of course, physiology/medicine.

It is my firm belief that there is a linkage between these seemingly disparate topics.

The COVID-19 pandemic was a human tragedy. However, it would be foolish not to admire the concerted research impetus it triggered and the astounding results of the biomedical effort that went into the development of vaccines. Lightning speed, this was *blitzkrieg* by any other name! It would have been preposterous indeed, had the discoveries leading to our mRNA vaccines been passed over in this year's Nobel Prize list. True to form, the ground-breaking work of Professors Karikó and Weissman has been justly recognised.

The past three decades have seen a welcome shift in the management of breast and testicular cancer. Governments in developed nations recognised that these cancers are very significant health disorders affecting millions worldwide. Strong partnerships between governmental and non-governmental organisations brought about much-needed change, such that the outlook of patients with these diseases has changed dramatically, for the better. Heightened awareness, dedicated multi-disciplinary teams and patient advocacy groups harnessed the advent of refined diagnostic modalities and elegant surgical, hormonal, biological, chemotherapeutic and radiotherapeutic options to curb the suffering and to effect a cure for millions. This was no miracle! This effort would not have been possible without throwing money at these diseases. The insatiable research effort has been and continues to be considerable.

In developed nations, birth rates are down and life expectancy is up. As a result, populations are ageing and to cite Malta as one typical example, the older person population currently making up a fifth, will in the very near future account for a fourth of the total. Ageing is a reality, not a challenge. When one talks of "challenges" posed by this demographic truth, then it is a small step to slip along the discriminatory slide of ageism.

One does not need to be some maverick statistician to appreciate the facts. Populations are getting older, fact. Increasing age is the overwhelming non-modifiable risk factor for dementia, fact. The prevalence of dementia will double 10 years earlier than previously expected, fact. Despite the rising incidence of dementia we do not know much about it, fact. We are not throwing enough money at it, fact. We only have four drugs available in the EU, and these may or may not slow progression. These are not curative treatments despite being around woefully long. Donezepil, memantine, galantamine and rivastigmine were developed between 1956 and 1985!

Our efforts to treat the various types of dementia are laudable but nowhere near what is needed to defeat rather than dent this condition. We do well to improve care and standards, support persons and their relatives, train the workforce and develop documents. But these are coping strategies even if they profess to be "long-term". Governments and private enterprises have to recognise that this reality is here, it is not just on the way. We have to come together and pool resources to firmly work out the pathogenesis and effect a cure. Nothing else will work; I am a firm believer that dementia is one of the main true health disorders of this century. So why not engage with the big guns, the pharma giants, the big tech companies including Google, Microsoft, and Apple? How's that for a noble corporate responsibility initiative?

I started with October, money matters in the budget, worldwide campaigns against disease and the UN Day for Older Persons. Talk and strategies are cheap. The big guns need to start gunning and they should be gunning for the right reason. Humankind needs to evolve and dump the distractions offered by conflict and war. Yes, we need more Nobel Prize winners. Eager minds of tomorrow coming up with discoveries that will enable the effective development of a cure for dementia. We can and we will.

LEQVIO®

PRESENTATION: Leqvio 284 mg solution for injection in prefilled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. ♦*Missed doses*: If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. ♦ *Treatment transition from monoclonal antibody PCSK9 inhibitors*: Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. ♦*Elderly, hepatic impairment, renal impairment*: no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment. ♦*Paediatric population*: The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. ♦*Method of administration*: Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: ♦*Haemodialysis*: The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. ♦*Sodium content*: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: ♦There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. ♦It is unknown whether inclisiran is excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. ♦No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common*: Adverse reactions at the injection site.

LEGAL CATEGORY: POM PACK SIZES: Pre-filled s y ringe: x 1 p re-filled syringe. Pre-filled syringe with needle guard: x1 prefilled syringe with needle guard.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2

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2022-MT-LEQ-24-MAR-2022

References: 1. Novartis Europharm Ltd. Leqvio Summary of Product Characteristics.

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LEQVIO® inclisiran

LEQ AD1 08/23 MT

Issue Guide

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YELLOW-EDGED MORAY
[Gymnothorax flavimarginatus] taken on the 31 Wreck, Comino.
Sony RX100M3 / 24mm / f3.5 / ISO800 / 1/30sec.
Credits: Lee Jellyman

DR PHILIP BORG

Longevity Medicine - Is This the Future of Healthcare?

Since 1900 the global average life expectancy has more than doubled, and is now above 70 years, due to major advances in healthcare such as antibiotics and vaccines as well as improvements in housing and education.

Although lifespan has increased by 30 years since the 1950s, healthspan (number of years lived in good health or free of disease) has not increased at the same rate.

In fact, in 2020, the gap between lifespan and healthspan in Europe and the UK was 15 years for males and 19 years for females. This means that the average person people is living one-fifth of their life with a chronic health condition.

The increase in lifespan because of modern medicine is mostly due to reduction in deaths from infection through the development of antibiotics, and reduction in deaths from trauma through better access to emergency medicine. Global mortality rates due to causes other than contagious diseases have not changed much since 1900.

Modern medicine (reactive medicine) is excellent at tackling diseases which need fast treatment when a symptom develops. Examples of reactive medicine include doctors prescribing antibiotics for a bacterial infection and orthopaedic surgeons repairing bone fractures after a traffic accident. Reactive medicine is not as effective in the treatment of the chronic diseases of ageing.

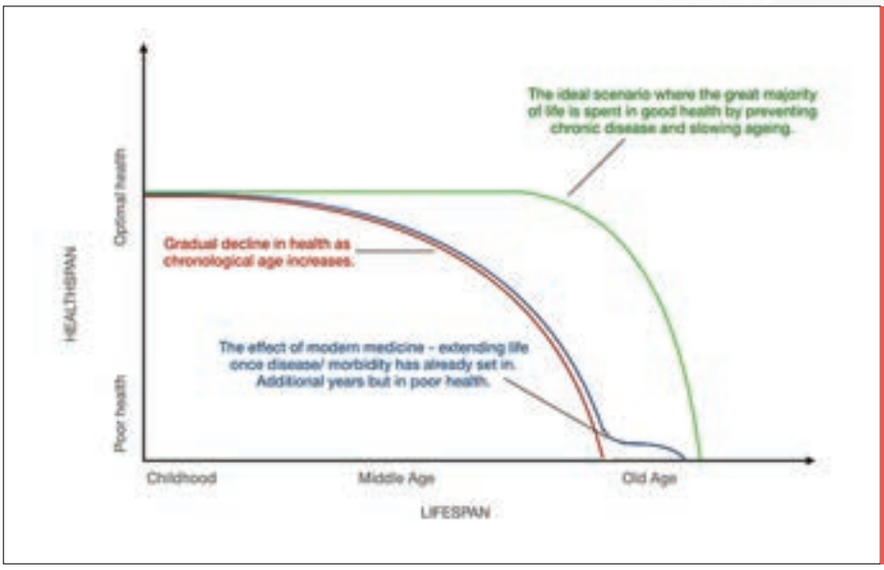
Too often, by the time symptoms of a chronic disease appear, the patient has already suffered an irreversible significant decrease in their healthspan.

THE CHRONIC DISEASES OF AGEING

In recent years, changes in our environment and the way we live have also led to an increase in diseases that were uncommon before the 1900s. For example, the risk of dying of cancer was 5% before 1900 and has increased to 25% today. The current leading cause of death - heart disease - was also an uncommon cause of death before 1900. This is partly due to the fact that people are living longer, therefore increasing the chance of developing chronic disease, however there is a strong link between lifestyle choices and development of these diseases.

So what are the chronic diseases associated with ageing? 80% of deaths in non- smokers above the age of 50 are due to 4 chronic diseases:

- Cardiovascular disease
- Cancer
- Alzheimer's disease (and other neurodegenerative diseases)
- Metabolic diseases (diabetes and other related diseases)



THE 3 MOST IMPORTANT LIFESTYLE FACTORS WE CONTROL ARE EXERCISE, NUTRITION AND SLEEP ... SLEEPING 7-8 HOURS A DAY INCREASES LIFE EXPECTANCY AND DECREASES THE RISK OF DEVELOPING ALZHEIMER'S DISEASE

The increasing gap between lifespan and healthspan suggests that modern reactive medicine is helping people to survive longer with disease and disability, rather than increasing good quality years of life.

Longevity medicine aims to prevent the onset of these diseases and screen early for signs of disease in the asymptomatic phase when medical and lifestyle interventions can be most effective in maintaining healthspan.

Our lifespan is partly influenced by our genetics, which we cannot control. We can, however, increase our lifespan and healthspan through the lifestyle choices we make.

The 3 most important lifestyle factors we control are exercise, nutrition and sleep.

Maintaining fitness and muscle mass as we age reduces the risk of developing the diseases of ageing. Aerobic and resistance (weight) training are equally important in maintaining cardiac function, mobility, stability, insulin sensitivity, and brain health. In addition, focusing on eating minimally processed, whole foods with a bias towards a plant-based diet and ensuring sufficient protein intake supports the slowing of the ageing process. Sleeping 7-8 hours a day increases life expectancy and decreases the risk of developing Alzheimer's disease.

We should also consider the economic cost of public healthcare, which is continuously rising. 15% of the European population aged 65 and over consumes 60% of healthcare resources. In developed countries, the over 65 age group accounts for 40-50% of healthcare spending and their per capita healthcare costs are three to five times higher than those under 65. Projections for Europe forecast that the population over 65 years will have increased from around 16% in 2000 to 23% in 2025 and will increase further to 30%in 2050, and, that healthcare costs are likely to grow at an average annual rate of 5-6%, most of this cost attributed to increasing ageing. Through a change in practice from the current model of reactive medicine to longevity medicine, it may be possible to maintain health and reduce healthcare costs.

We all want to live a long life in good health - maintaining mobility, independence and mental well-being by extending the period of your life in which you are physically active, cognitively sharp and socially present.

There is no secret formula to a long and healthy life. Simple lifestyle changes as well as early screening will increase your lifespan and healthspan.

DR ANNA MARIA FENECH MAGRIN

Hyperhidrosis with a Focus on Primary Axillary Hyperhidrosis

ABSTRACT

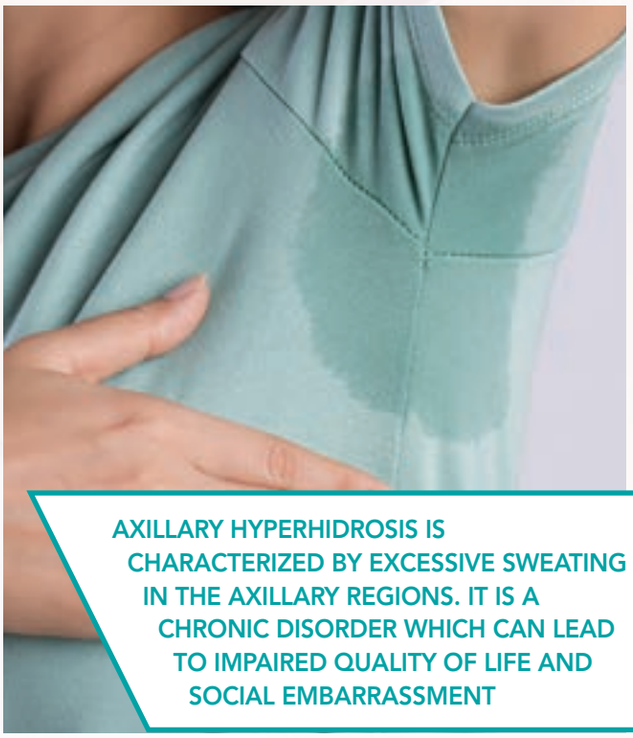
Axillary hyperhidrosis is characterized by excessive sweating in the axillary regions. It is a chronic disorder which can lead to impaired quality of life and social embarrassment. Identifying the condition is important so it can be safely and effectively treated. Evidence shows that Botulinum toxin is a safe and effective method of treatment for focal hyperhidrosis and provides longer-lasting results than topical treatments without the need of invasive surgery.

INTRODUCTION

There are two main types of human sweat glands. The eccrine sweat glands are mainly responsible for thermoregulation over various body surfaces. On the other hand, apocrine sweat glands are restricted to specific areas such as the axillae, anogenital region and areolae, which produce an odourless secretion which then develops malodour through bacterial decomposition.

Sweating is necessary for thermoregulation, however, for 1 – 3% of the population it can cause difficult daily functioning as the body produces more sweat than is needed for normal thermoregulation. When this occurs, it is called hyperhidrosis.[1]

Hyperhidrosis is a condition that causes excessive sweating, usually from the palmar, plantar and axillary surfaces. The underlying mechanism is thought to be a sympathetic overstimulation of the eccrine sweat glands. Hyperhidrosis can be primary or secondary. Primary hyperhidrosis affects around 1% of the general population. It is inherited as an autosomal dominant genetic trait and it usually starts during adolescence and sometimes even before, during childhood. It is bilaterally symmetrical, and commonly affects the axillae, palms, soles or craniofacial regions.[2] Severely affected patients may have secondary microbial infections, as well as other skin changes including maceration. They may be socially stigmatized and it can lead to substantial emotional and physical impairment in a person's occupation and social life. The negative effect on quality of life (QoL) from hyperhidrosis is similar to or greater than that of other dermatologic conditions, including severe acne and psoriasis.[3,4]



AXILLARY HYPERHIDROSIS IS CHARACTERIZED BY EXCESSIVE SWEATING IN THE AXILLARY REGIONS. IT IS A CHRONIC DISORDER WHICH CAN LEAD TO IMPAIRED QUALITY OF LIFE AND SOCIAL EMBARRASSMENT

Secondary hyperhidrosis typically occurs at a later age. It is usually unilateral, asymmetric, generalized and also, present during sleep. It is likely to occur due to an underlying medical condition such as diabetes mellitus, neurological disease, cardiovascular disease, hormonal changes like menopause, malignancy, infection and febrile illness. It can also be caused by a medication adverse effect.[5]

Excessive sweating can not only have an emotional and psychological impact, but it can also lead to physical complications. These include an increased risk of dermatophytosis, keratolysis and it can also be associated with atopic dermatitis.

DIAGNOSTIC APPROACH FOR PRIMARY HYPERHIDROSIS

Patient History and Examination

Diagnostic criteria for diagnosing focal primary hyperhidrosis have been developed (Table 1). To make a diagnosis in the clinical setting, secondary hyperhidrosis has to be excluded first. Therefore, a detailed clinical history and examination are very important. This includes a detailed medical and surgical history and medication history. One should enquire about neurological and endocrine symptoms like fatigue, weight gain, night sweats, headaches, vision changes, weakness, paresthesia, polyuria, polydipsia and fever. This will help in determining what further tests are needed in case of secondary hyperhidrosis.[5]

Table 1. Diagnostic criteria for focal primary hyperhidrosis.
Source: Hornberger J et al.[5]

Diagnostic criteria
Focal, visible, and excessive sweating for ≥ 6 months without aetiology with two or more of the following: 1. Bilateral and symmetrical sweating 2. Impaired daily activities 3. Occurring at least once weekly 4. Onset < 25 years of age 5. Positive family history 6. Cessation while asleep

On examination, one should observe the pattern of sweating and inspect the sites of the patient-reported hyperhidrosis. The neck should be palpated to check for any lymphadenopathy or thyroid enlargement. The blood pressure should be measured, and baseline laboratory tests carried out if indicated.[6]

The Starch-iodine Test

This is an assessment tool first described by Dr Victor Minor, a Russian neurologist, in 1928. It qualitatively identifies the hyperhidrotic skin areas. After the skin is cleaned and left to dry, it is then covered in 1 – 5% iodine solution. This is allowed to dry and starch powder is brushed on the area. The light brown iodine colour turns to dark purple as an iodine-starch complex forms in the liquid medium as the sweat comes to the surface,[7] determining the area requiring treatment.

Patient-reported Outcome Measures (PROM)

There are several patient-reported outcome measures. The most common one which is used in the clinical setting is the Hyperhidrosis Disease Severity Scale (HDSS). Besides being used to evaluate the presence and severity of axillary sweating for clinical studies, it is also used to evaluate hyperhidrosis for botulinum toxin treatment.[8]

Table 2. Hyperhidrosis Disease Severity Scale (HDSS).
Source: Lowe NJ et al.[8]

Question: How would you rate the severity of your hyperhidrosis?	Score
My underarm sweating is never noticeable and never interferes with my daily activities.	1
My underarm sweating is tolerable but sometimes interferes with my daily activities.	2
My underarm sweating is barely tolerable and frequently interferes with my daily activities.	3
My underarm sweating is intolerable and always interferes with my daily activities.	4

TREATMENT OF HYPERHIDROSIS

Treatment modalities that have shown a rate of reduction of sweat production include:

- Iontophoresis
- Topical application of aluminium chloride
- Administration of anticholinergic agents
- Beta-blockers
- Surgical removal of sweat glands
- Sympathectomy
- Laser or ultrasonography therapy
- Microwave thermolysis
- Intradermal injection of botulinum toxin type A.

TREATMENT WITH BOTULINUM TOXIN A, FOCUSING ON AXILLARY HYPERHIDROSIS

Mode of Action

Botulinum toxin A (Btx-A) works by blocking neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurons.[9] The mechanism of action of Btx-A in focal hyperhidrosis is still not fully understood, but it is most certainly different than that in muscle spasms.[10]

DIAGNOSTIC CRITERIA FOR FOCAL PRIMARY HYPERHIDROSIS [ARE] FOCAL, VISIBLE, AND EXCESSIVE SWEATING FOR ≥ 6 MONTHS WITHOUT AETIOLOGY, WITH TWO OR MORE OF THE FOLLOWING: BILATERAL AND SYMMETRICAL SWEATING, IMPAIRED DAILY ACTIVITIES, OCCURRING AT LEAST ONCE WEEKLY, ONSET < 25 YEARS OF AGE, POSITIVE FAMILY HISTORY AND CESSATION WHILE ASLEEP

Sweat glands have a different nerve supply (sympathetic sudomotor C fibres instead of cholinergic α-motor neurons). The inhibitory action of Btx-A is not limited to the neuromuscular junction. The toxin also blocks the autonomic cholinergic fibres, including the sympathetic fibres to sweat glands. The effect of Btx-A on focal hyperhidrosis lasts longer (8-9 months) than on muscle spasm disorders (3-4 months).

In a study by Swartling et al.[10] palmar skin biopsies were performed on 26 hyperhidrotic patients before Btx-A treatment, and also on 11 controls. The aim was to study the effect of Btx-A on the size and innervation of sweat glands in patients with palmar hyperhidrosis. Biopsies were taken again one to six months after the injections. The sweat gland morphology was similar in patients and controls before the treatment.

After the treatment, the tubular dimensions remained the same, however, the lumen of the sweat gland appeared smaller. Also, staining showed that functional nerve growth diminished and therefore Btx-A therapy induces long-lasting functional denervation of the sweat glands.[10]

Safety and Efficacy

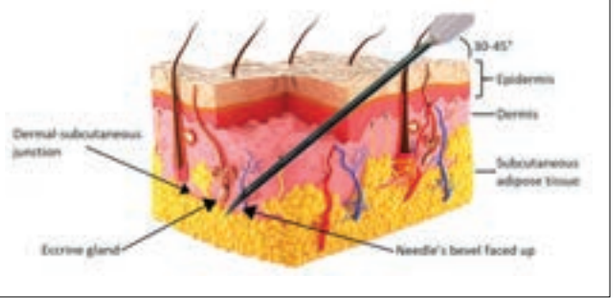
A 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety on 322 patients by Lowe et al. (2007) showed that Btx-A treatment effectively reduces the symptoms of primary axillary hyperhidrosis. It is well tolerated and has a safety profile similar to that of a placebo.[8]

Therapeutic Approach

The sweat glands are targeted when Btx-A is injected intradermally at the dermal-subcutaneous junction, around 2mm deep in the axilla. A hypodermic needle is oriented at 30° to 45° to the skin surface with the bevel facing up.[2]

At least a total of 50 units of Btx-A per axilla are needed to treat hyperhidrosis. The injections are done in 10 to 20 sites in each axilla, 1.5 to 2.5cm apart. After the treatment, the effect is commonly observed within 7 to 10 days. It lasts for about 6 to 10 months.[11]

Figure 1. The proper technique for injecting botulinum toxin for the treatment of primary hyperhidrosis.
Source: Nawrocki S et al.[2]



Adverse effects observed when treating axillary hyperhidrosis with BTX-A include pain, hematomas, bruises, headaches, muscle soreness, local pruritis which is mild, and also, compensatory sweating in 5% of patients.[12]

When treating palmar and plantar hyperhidrosis, higher doses of BTx-A are required i.e. 75 to 100 units per hand/foot are commonly used. These are uniformly distributed into 5 to 50 sites spaced 1 to 1.5cm apart. The digits usually require 2 to 3 injections each.[13,14] Of note is the fact that BTx-A treatment for palmar hyperhidrosis is very painful.

Contraindications

BTX-A should not be used in pregnant or breastfeeding women. It should also not be used if the patient has a known hypersensitivity to any of the formulation components, if the area of injection is infected, in patients suffering from secondary hyperhidrosis, patients who have undergone surgical removal of sweat glands, and patients with blood-clotting disorders.[11]

CONCLUSION

In conclusion, treatment with botulinum toxin produces a significant reduction in the severity of primary axillary hyperhidrosis and evidence shows that this treatment has a high safety and efficacy profile.

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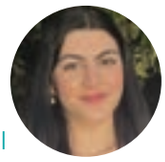
Science in the City 2023



YLENIA XERRI

On 29 September, MPSA had the opportunity to form part of Science in the City which was held in Valletta. This is an annual event that is looked forward to by many science enthusiasts.

The Science in the City Festival always aims to engage the community in science and creativity. The theme chosen for this year's edition was "Changemakers". This particular theme was chosen with the scope of using research-based knowledge and creativity to overcome the political, social, environmental and technical challenges that confront us.

MPSA set up a stand where blood glucose and blood pressure testing were carried out. This was the perfect opportunity for pharmaceutical students to apply their knowledge and educate the public about the importance of frequent monitoring, risk factors associated with high glucose levels and high blood pressure, as well as lifestyle modifications to maintain normal blood glucose and blood pressure levels.

A genetic taste test was also carried out. Phenylthiocarbamide taste strips were handed to volunteers who were instructed to place the strip on their tongues for a few seconds. Some people tasted the strip and others didn't. Different responses were obtained due to the *TAS2R38* gene. The *TAS2R38* gene encodes for the *TAS2R38* protein, which is a bitter taste receptor. Different genotypes of *TAS2R38* exist which results in different tasting abilities. PTC from the taste strip binds to the protein if present and a person will taste it. If the protein is not present, PTC will not bind and a person cannot taste it. Out of the people who tasted the strip, some tasted the strip more bitter than others. People who are homozygotes for the dominant allele produce either more proteins or proteins with more binding sites available to the PTC, thus the strip tastes more bitter. The purpose of this activity was to highlight the significance of individual genes to personalised treatment, and emphasise the shift from a 'one-size-fits-all' approach towards a personalised medicine approach. Other interactive games were carried out for children such as quizzes and puzzles about pharmacy terminology and the human body.

Through this event, apart from putting knowledge into practice, MPSA had the chance to interact with students from other student organisations and researchers, who all share the same passion for science. Overall, this event was a successful one with a great turnout.

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DR MATTHEW PIZZUTO, DR DANIEL CILIA, PROF. ROBERT SCIBERRAS

Lost to Follow-Up: A Challenging Case of Tuberculosis

ABSTRACT

We present a case of a 27-year-old Sudanese male who, on presentation for alcohol intoxication and a lacerated wound over his left lower limb, was found to have an incidental opacity in his left lung which was further characterized by a computed tomography (CT) scan. Testing on a bronchoalveolar lavage sample revealed *Mycobacterium tuberculosis*. After an uneventful admission, the patient's management plan faced issues with compliance, as the patient was expelled from his temporary social housing arrangement and failed to attend his follow up clinics.

Key Words: Tuberculosis, Multidrug Resistance, Direct Observed Therapy.

INTRODUCTION

Despite being a curable and preventable disease, Tuberculosis (TB) continues to have a significant burden in terms of morbidity, mortality and cost. The incidence across the different continents ranges from 26 to 226 cases per 100,000.[1] Direct Observed Therapy (DOT) is a strategy currently endorsed by the World Health Organisation and has five elements:

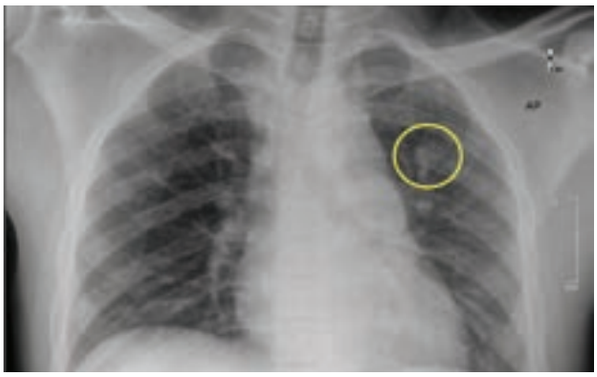
- Political commitment
- Microscopy services
- Drug Supplies
- Surveillance and monitoring systems
- Direct observation of treatment.

DOT aims to achieve two main goals, ensuring that a patient completes his therapy to cure and decreasing multidrug resistance in the community.[2]

CASE PRESENTATION

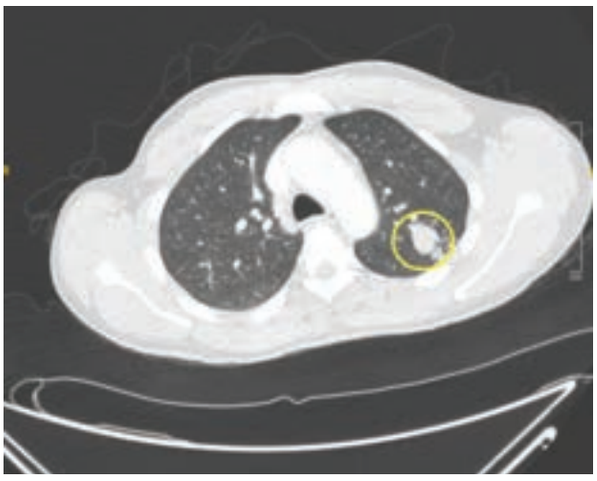
A 27-year-old Sudanese male was brought to the Emergency Department at Gozo General Hospital in view of alcohol intoxication and a lacerated wound over his left calf. The patient was unable to recall the events that occurred leading up to his presentation. Radiographs of the left lower limb confirmed a fracture of the middle portion of the left tibia. As the patient was a heavy smoker and worked as a plasterer, a chest radiograph was taken as part of the pre-operative assessment for intramedullary nailing of the fracture. This revealed a two centimetre round opacity in the middle zone of the left lung field (Figure 1).

Figure 1. Chest radiograph showing a two centimetre opacity in the middle zone of the left lung field



In view of the Chest X-Ray findings, a CT scan of the thorax was performed which showed an 18 millimetre by 16 millimetre low-intermediate density, tubular nodule in the apical segment of left upper lung (Figure 2). This was associated with a nine millimetre prominent lymph node in the aortopulmonary window.

Figure 2. A CT scan of the thorax showing a nodule in the apical segment of the left upper lung.



Efforts to retrieve his medical history since he came to Malta, four years prior to his admission, did not yield any relevant results, with no previous chest X-Rays, and only a few blood investigations taken the previous year for an intoxication episode.

Routine bloods were taken during this admission. Both HIV and a Hepatitis screen were negative, with no recorded elevations in CRP. The Liver Function Tests (LFTs) were normal except a marginally high gamma-glutamyl transferase (GGT), probably due to chronic alcohol use. All other routine blood investigations were otherwise unremarkable.

The patient underwent left tibia intramedullary nailing of the fracture and was discharged a few days later and an appointment was made for a bronchoscopy, which was carried out two weeks later. Bronchoalveolar lavage and bronchial brushings samples were taken and further investigated.

Microscopy of the samples revealed no abnormalities, however three weeks later, liquid culture revealed acid-fast bacilli which were confirmed to be *Mycobacterium tuberculosis*. The patient was traced and informed. He was then admitted to an isolation room for treatment. The patient's details were passed to the Public Health Department for disease notification purposes and contact tracing. The patient was found to be stable, with no complaints, and started on the following medications:

- Rifampicin 600mg daily
- Pyrazinamide 2g daily
- Ethambutol 1g daily
- Pyridoxine 10mg daily

The patient's admission was uneventful and after the 14th day, he wished to be discharged against medical advice. The case was discussed with Infection Control who informed the medical team that since 14 days of quarantine had elapsed, it was safe for the patient to exit quarantine. The details of the patient were forwarded to Public Health for follow-up and the patient was discharged to the community.

The patient failed to attend his medical outpatients and respiratory outpatients appointments, only to return to the Emergency Department a few weeks later after being referred from a health centre. The patient had been expelled from his temporary social housing arrangement soon after discharge in view of a recurrent intoxication issue and ended up without a permanent residence. The patient stopped his anti-tuberculous medication soon after being expelled. This case was re-discussed with Public Health, who informed that the patient should be readmitted and restarted on the same anti-tuberculous medications as previous.

During his second admission, together with the social workers, discharge liaison nurse and members from the public health team, a temporary social housing arrangement in Malta was found for the patient. This is important since the patient would have a residence where he could sleep and eat, as well as have DOT carried out, as part of the management plan of TB. This will help prevent of the development of Multidrug-Resistant Tuberculosis (MDR-TB).

DISCUSSION

Incidence and Aetiology

TB is an infectious bacterial disease caused by *Mycobacterium tuberculosis* affecting an estimated 9.9 million persons in 2020, of which 1.49 million died.[3] The infection is transmitted between humans via the respiratory route as an aerosol.[4] Approx. 10% of infected individuals progress to active TB infection during their lifetime, while the remainder successfully contain their infection, with the pathogen remaining in a latent state for many years in a significant proportion of these patients. This carries the risk of reactivation and disease.[5]

Treatment and Multidrug-Resistant Tuberculosis

The treatment of TB requires the use of multiple drugs for many months, which presents itself with a challenge, especially in cases such as the one presented here, where communication barriers and the lack of a permanent residence were present. The importance of this regime is of utmost importance, as failure in compliance may result in the development of MDR-TB, which requires longer treatment regimens consisting of medications which are more expensive and have more significant adverse reaction profiles.[5]

MDR-TB is TB that is resistant to at least both rifampicin and isoniazid, and accounts for 4.7% of all persons infected with TB, 3.3% of persons who are newly diagnosed with TB and for 18% of persons who were previously treated for TB.[1]

CONCLUSION

As demonstrated by our case, infection with TB and the risk of the development of MDR-TB is a reality, even locally. We wish to highlight the importance of a multi-disciplinary approach to DOT and regular follow-up as part of the management of TB.

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DR STEPHEN BRINCAT

Saint James Hospital Introduces New Technology to Optimize Breast Cancer Surgery

A Very Brief History of the Surgical Management of Breast Cancer

Man has been struggling to treat cancer long before we knew of the existence of DNA, genes, mutations, and the whole complex gamut of changes that lead to cancer.

The best that could be done until very recently was to try and cut it out. This approach presented many problems.

First, most patients with cancer who were heroic or desperate enough to submit to the surgeon's knife were already beyond cure.

Secondly most cancers were not externally visible and many of those that were e.g. head and neck cancers were inoperable. Having got beyond these two issues, many subjected to surgery without anaesthesia died of shock, and of those who survived many died of infection. The successes were anecdotal. With the advent of anaesthesia and anti-sepsis, things got better but there was still a poor understanding of the biology of cancer.

Halstead's radical mastectomy which was the accepted surgical gold standard for the treatment of breast cancer between the late 19th and mid-20th century and beyond, subjected thousands of women to a mutilating procedure based on the false premise that the more healthy tissue that was removed around the tumour, the better the outcome. I have a depressing image of these women from my student and junior doctor days. Today we know that outcome is largely dependent on two factors, tumour biology which we cannot influence and stage at diagnosis and treatment which we certainly can.

The radical mastectomy removed the whole breast as well as the pectoral muscles, leaving a chest wall covered by skin, later made thin and atrophic by the addition of radiotherapy. The removal of the pectoral muscles weakened the arm. But this was only one part of the operation. The accompanying axillary dissection was all too often followed by the development of gross lymphoedema of the upper limb, producing a grotesque, heavy, uncomfortable limb prone to recurrent infections which only made the swelling worse.

Large, randomized trials carried out in the 1970's and 1980's clearly demonstrated that a simple mastectomy was no worse than a radical one, thus sparing the pectoral muscles, and that for the smaller tumours, which today constitute the majority in Malta and the Western world, a wide local excision of the primary tumour followed by radiotherapy produces the same local recurrence rate as a simple mastectomy. There still remain some indications for a total mastectomy for example multiple tumours in the same breast or a large tumour in a small breast but these now constitute a minority.

This, combined with techniques of breast reconstruction both at the time of primary surgery or later, has greatly altered the cosmetic and psychological outcome of breast cancer surgery. But what about the second part of the operation, that on the axilla? Once the procedure to remove the primary had become a relatively minor one, the axillary dissection came to present the main cause of morbidity.

NEW TECHNOLOGY TO OPTIMIZE BREAST CANCER SURGERY

The need to carry out an axillary dissection has today been drastically reduced by the introduction of Sentinel node biopsy. Unless there is gross involvement of the axilla with cancer, the axillary part of the operation is largely a staging procedure rather than a therapeutic one. It gives us information on one important prognostic criterion, namely whether the cancer has affected the axillary nodes and to what extent. On this basis (and others), the oncologist will decide the nature of post operative systemic treatment and areas to be radiated.

That information can be equally obtained by removing and examining the axillary Sentinel node (or 2 or 3 nodes). This is the node/nodes to which the tumour primarily drains. If negative, the axilla is taken as clear. If positive, one can proceed to an axillary dissection in a positive node counting exercise, but if imaging does not indicate gross disease even this is largely unnecessary.

SAINT JAMES HOSPITAL HAS NOW INTRODUCED A SYSTEM THAT DOES AWAY WITH THE RADIOISOTOPE AND INSTEAD USES A MAGNETIC LIQUID TRACER (MAGTRACE®)

As the axilla contains between 20 and 40 nodes, the problem lies in finding the right one to remove and examine. The first technique to resolve this problem involved injecting a tracer of Methylene Blue into the breast and finding the blue dye in the axilla. Next came an injection of Technetium whose radioactive presence in the sentinel node could be detected by a radioactivity probe. This is still often combined with the Methylene Blue technique as a double check.

Saint James Hospital has now introduced a system that does away with the radioisotope and instead uses a magnetic liquid tracer (Magtrace®). This is injected, conveniently, with the patient under anaesthesia twenty minutes prior to starting the surgery. The sentinel node/nodes are detected by a magnetic probe as well as secondarily by the colour change (brown) they undergo when they take up the tracer. The latter is more of a confirmatory feature. The tracer can be administered up to 30 days prior to surgery though logistically and for the patient's comfort it is more sensible to do this immediately prior to surgery.

It is a system now widely used in several Oncology centres in over 50 countries including the Royal Marsden hospital but is a first for Malta.

DR ALFRED GRECH, DR MARIO FARRUGIA, DR MICHAEL BALZAN

Models for Translational Research of Human Diseases

ABSTRACT

Human disease models, including cell models, are important platforms in translational research studies to understand the pathophysiology of human diseases. The subject is vast as many models and diseases are involved. This essay will focus on the following models i.e. *Saccharomyces cerevisiae* (baker's yeast), *Schizosaccharomyces pombe* (fission yeast), *Caenorhabditis elegans* (roundworm), *Drosophila melanogaster* (fruit fly), *Danio rerio* (zebra fish) and *Mus musculus* (laboratory mouse), which are being used in such human diseases such as cancer, metabolic diseases, inflammation, infection, and neurodegenerative conditions. With the impact of CRISPR and next-generation sequencing technologies, disease modelling is stepping up the understanding of molecular mechanisms of human diseases. This in turn is helping in the theranostic management (diagnosis, prognosis and therapy) of the latter and paving the way to more personalized precision medicine.

INTRODUCTION

A disease model is an organism or its cells that display a pathological process that is observed in the human disease. Examples of well-known model organisms that will be discussed in this essay are *Saccharomyces cerevisiae* (baker's yeast), *Schizosaccharomyces pombe* (fission yeast), *Caenorhabditis elegans* (roundworm), *Drosophila melanogaster* (fruit fly), *Danio rerio* (zebra fish) and the laboratory mouse (*Mus musculus*). There are many others of course.

Indeed, human disease models are many and diverse and their utility depends on the investigations which need to be carried out. The choice of the model exploited is generally a trade-off based on the degree that the model mimics the disease and how easy the model platform can be manipulated. Normally, these organisms have certain common characteristics and Table 1 lists some of them.

Table 1. Some common characteristics of disease models.

Studied extensively
Relatively easy and cheap to maintain and breed in large numbers under laboratory conditions
Relatively short generation time (interval from birth to reproduction capability)
DNA can be genetically mutated, thus allowing studies of a specific characteristic or disease
Similar genes to humans (homology)

Homology refers to the similarity between genes in different taxa. A gene is called homologous because it has been inherited in species that have evolved from a common ancestor. Homologous genes code for homologous proteins that have similar functions. When it comes to human disease models, the models are used because they have human homologous genes. And the more this homology is, the more chance that the research could (but not always) be translated to humans.

Human disease models are becoming increasingly important to understand the fundamentals of biology and medicine and are paving the way to better understand genetic susceptibility to disease. Methods that target and edit genes are enabling researchers to create mutant alleles of the genes under scrutiny and so help in studying gene function. Unprecedented advances in genomics and gene sequencing (like next-generation sequencing technology) are also helping in the translation of research findings using model organisms. Other platforms that are helping researchers to interrogate more precisely gene function include CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene-editing technology, knockout methods, and the availability of tools to mine data from several data banks (genomic, transcriptomic, proteomic, metabolomic) from various organisms including those of humans. This integration allows more precise translation from models to humans.

Translation is not always possible due to various reasons. One reason is that biological systems exhibit complexity and redundancy. Another two reasons are that human disease has its own pathophysiological heterogeneity and each disease encompasses subpopulations of patients with somewhat different pathophysiological mechanisms. Also, many candidate molecules in clinical trials fail due to pharmacokinetic challenges relating to absorption and distribution in the target organ.

Yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)

Yeasts are simple eukaryotes. The main yeasts that are valuable, versatile and powerful disease model organisms are *Saccharomyces cerevisiae* (baker's yeast) and *Schizosaccharomyces pombe* (fission yeast). Their genetic tractability, short generation time and easy and cheap genetic manipulations are pivotal in the large worldwide network of research to understand gene variants of different human diseases. *Saccharomyces cerevisiae* was the first eukaryote to have its genome fully sequenced and functionally annotated. This led it to serve as a leading reference genome when annotating new genes and when studying other complex organisms.

Melanie Lee and Paul Nurse (1987)[1] published a seminal paper on *Schizosaccharomyces* revealing work on a key regulator of the cell cycle, specifically CDK (cyclin-dependent kinase). This earned Nurse a Nobel Prize in Physiology or Medicine in 2001, which was shared with Tim Hunt and Lee Hartwell. Elizabeth Blackburn, Carol Greider and Jack Szostak also used yeast and were awarded a Nobel Prize in Physiology or Medicine in 2009 for their work on telomere and telomerase. These molecular underpinnings using yeast later had clinical repercussions in cancer as cyclin-dependent kinases (and their partners, the cyclins) are molecular targets for treatment.

These unicellular eukaryotes are also important models to study aging and neurodegenerative disease like Parkinson's, Alzheimer's, Huntington's and motor neuron diseases. The pathological processes that underlie these conditions, namely impaired autophagic protein degradation, impaired mitochondrial function, deviant programmed cell death mechanisms, and misfolding and aggregation of culprit proteins, are all found in yeast.

Research using yeast is still ongoing. Indeed, the importance and function of the non-protein coding elements (once called the 'dark matter of the genome') of this eukaryotic genome are being found to be also essential to the fitness of the organism. Grech et al.[2] using saturating transposon mutagenesis, interrogated the *Schizosaccharomyces pombe* genome. They found that the transposon insertions had fitness effects in 80% of the noncoding regions. Specifically, they also found 85 necessary non-coding RNAs during the vegetative growth of the yeast and 218 during its ageing phase. Research similar to this has propelled more studies to underpin the functions of ncRNAs, and some discoveries have already been translated into the clinical setting as biomarkers and non-coding RNA-based therapy.[3]

Roundworm (*Caenorhabditis elegans*)

Caenorhabditis elegans is a nematode worm and it also has been used to study various human diseases. Table 2 shows the names of the researchers who won a Nobel Prize stemming from research using this worm. This goes to show the importance of this worm in research.

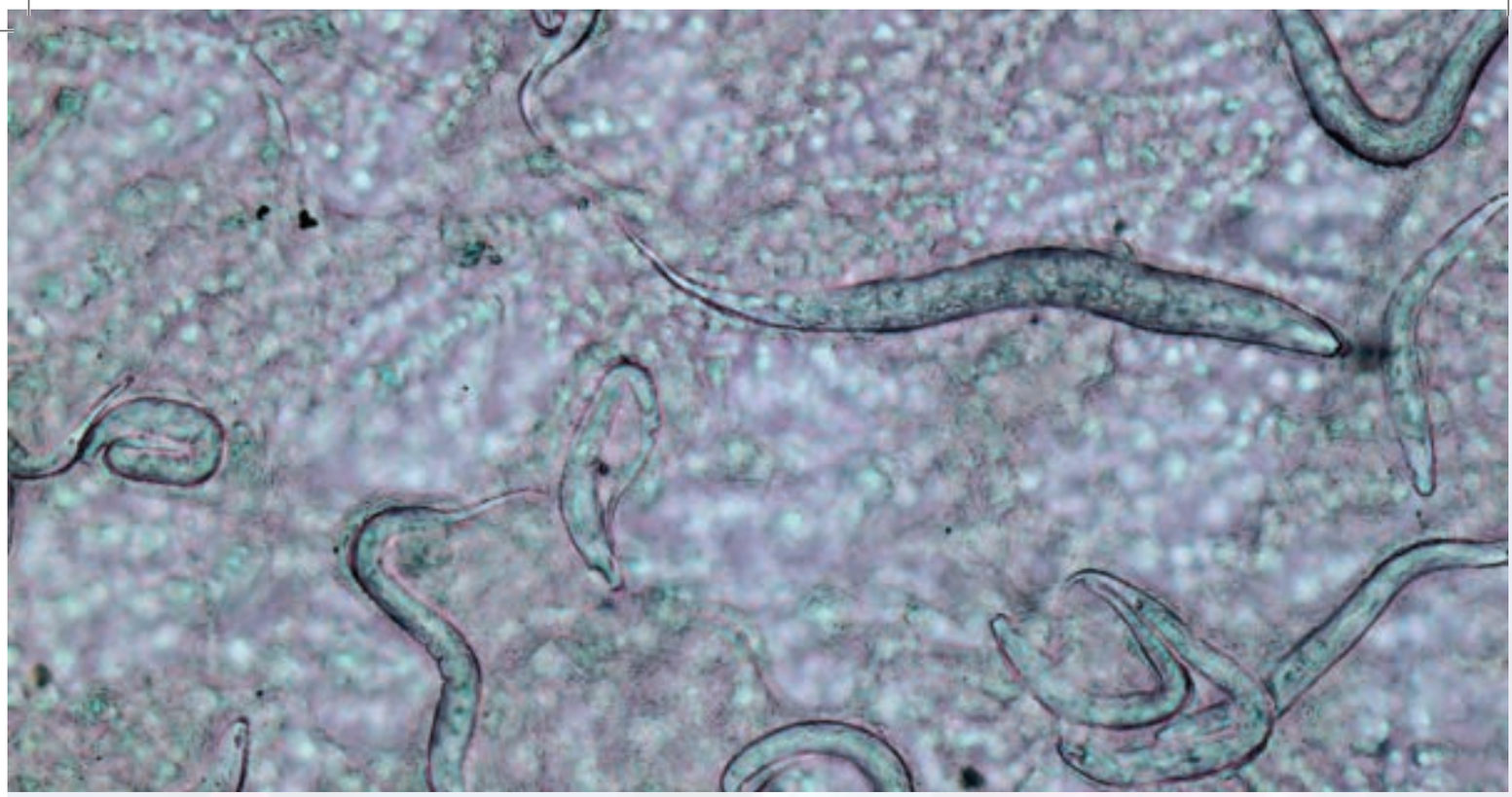
Table 2. Nobel Prize laureates and their discovery.

Year, Nobel Prize Winners	Discovery	Paper
2002, Sydney Brenner, Robert Horvitz and John Sulston	Developmental biology and cell death machinery	4,5,6
2006, Andrew Fire and Craig Mello	RNA interference (RNAi)	7
2008, Osamu Shimomura, Martin Chalfie and Roger Tsien	Green Fluorescence Protein (GFP)	8

Table 3 shows some of the diseases that this worm was used as a model.

Table 3. Selected studies using Caenorhabditis elegans.

Human Disease or condition	Study	Reference
Autism	Neuroligin dependence of social behaviour	9
Retinitis pigmentosa (RP)	Drug screening and identification of modifiers	10
Alzheimer's disease	Neuroprotective effect of human Vps41 protein	11
Parkinson's disease	Modulation of cholesterol metabolism in neurons	12
Oncology	Anti-cancer potential of etodolac, itraconazole, disulfiram and ouabain	13



Autism is characterised by disrupted social behaviour. Rawsthorne et al.[9] used *C. elegans* to study a gene that codes for neuroligin, which is associated with autism. Neurologin is a protein in the postsynaptic membrane involved in the connection of neurons at synapses. They found that neuroligin is specifically important in the recognition and processing of social signals.

Kukhtar et al.[10] used CRISPR/Cas technology to create mutant strains of *C. elegans* to target splicing-related genes associated with retinitis pigmentosa (RP). They tested a set of RNAi clones on these genes and found that their partial inactivation might alter the course of the disease. Also, they found that dequalinium chloride (an active ingredient in various medications) could be harmful to a type of RP.

In their study, Griffin et al.[11] compared two transgenic models of *C. elegans* to show the neuro-protective effect of human Vps41 (vacuolar protein sorting 41), which is a protein involved in the trafficking of lysosomes. Their work aimed to find targets that can halt the degeneration of neurons in Alzheimer's disease. On the other hand, through their findings using *C. elegans* as a model, Zhang et al.[12] showed that modulating cholesterol metabolism in neurons can reduce the neurotoxicity of alpha-synuclein. The latter, which are peptised, are the major components of Lewy bodies. They even propose this regulation as a prospective treatment for Parkinson's disease.

Medina et al.[13] used mutant strains of *C. elegans* and showed the anti-cancer potential of 4 drugs, specifically etodolac, itraconazole, disulfiram, and ouabain. Their investigation could lead to a drug repurposing strategy.

The immune system has two pillars, (i) innate immunity and (ii) adaptive immunity. Given that *C. elegans* has only the innate immune response, it has been used to study this response to pathogens. The standard feed for *C. elegans* is *E. coli*. The latter can be swapped with a pathogen like *Salmonella enterica*. Investigations of this setup showed an immune response of the host involving the p38 MAPK (mitogen-activated protein kinase) signalling cascade.[14] This pathway generates various biological effects in response to diverse external signals. The study also showed that the crucial factors for the virulence of *Salmonella Typhimurium* are an expression of PhoP/PhoQ and SPI-1 (*Salmonella* pathogenicity island 1).

In keeping with the fact that the ageing process is a common factor for many diseases, *C. elegans* has been exploited to study ageing, especially the use of anti-ageing drugs for a healthier ageing phenotype and lifespan modulation. Ziehm et al.[15] discuss a pipeline for candidate compounds including some repurposed drugs (like imatinib), with which further investigations could be used for healthier ageing in humans. Wang et al.[16] found anti-oxidant and anti-ageing effects in extracts from hawthorn berries. The hawthorn tree's berries and leaves have long been used in traditional medicine for their various health benefits. Wang et al. found that the lifespan of *C. elegans* was increased by 28% when treated with the extract and also improved resistance to stress caused by ultraviolet radiation and heat. They even proposed that these health benefits were mediated by the insulin/insulin-like growth factor-1 (IIS) signalling pathway. The latter connects nutritional status to important functions like growth, metabolism, reproduction and ageing. Such investigations are still at an early stage but they are being honed into better pipelines which will ultimately be translational for the benefit of humans.

Fruit fly (*Drosophila melanogaster*)

Table 4. List of Drosophilists who won a Nobel Prize.

Drosophilists who won a Nobel Prize	Discovery
Thomas Hunt Morgan	Chromosomes contain linear arrangements of genes
Hermann Joseph Muller	X-rays can cause mutations
Christiane Nusslein-Volhard Eric Wieschaus Edward B. Lewis	Genetic control of early development of the embryo
Jules A. Hoffmann	Activation of the Innate immunity
Michael Rosbash Jeffrey C. Hall Michael W. Young	Molecular mechanisms of circadian rhythm

Table 4 lists drosophilists who won a Nobel Prize. Again, this shows the importance of *Drosophila melanogaster*. Indeed, it is another extensively studied and tractable genetic model organism which underpins the molecular pathways of a wide range of human diseases. Importantly, about 75% of genes that cause disease in humans have a functional homolog in this fly.

Drosophila has been used to study epigenetics associated with ageing and cancer. It is also being exploited in nutrition research to study the molecular mechanisms of diabetes and obesity. Moreover, Drosophila is used in research associated with COVID-19. It has also been exploited for drug discovery and repurposing. For example, Alli et al. [17] found a potential anti-lithogenic compound, arbutin, for kidney stones. Bangi et al.[18] fished a two-drug cocktail of trametinib plus zoledronate as a personalized treatment for a patient with metastatic colorectal cancer showing a KRAS (Kirsten rat sarcoma)-mutant phenotype. KRAS-mutant phenotype is associated with marked aggressiveness and poor prognosis. Bangi et al. analysed the cancer's genome and fished 9 perturbed culprit genes. A transgenic model of the fly was developed containing the mutated orthologs of the 9 perpetrator genes. Subsequently, a robotic-based screening was employed and this led to the identification of trametinib plus zoledronate as a potential treatment. The patient showed an acceptable significant response. In their paper they propose that such a personalized approach can be a way forward for refractory cancer, offering hope for patients with an otherwise poor prognosis.

Zebrafish (*Danio rerio*)

Another relevant model which has gained prominence in biomedical research of human disease is the zebrafish model. This is because its biology permits research of all developmental stages. Indeed, the internal organs can be visualised non-invasively as its embryos and larvae are optically transparent and allow real-time imaging of normal and pathological development. In fact, every cell can be seen and studied. Another advantage is that one can easily create an efficient and cost-effective system because zebrafish are relatively easy to maintain in the laboratory in large numbers. Importantly, like the other disease models mentioned so far, there is a high conservation of genes between the human genome and that of the zebrafish. Specifically, 70% of human genes have a counterpart in the zebrafish. And considering human disease genes, 84% have a zebrafish counterpart.

Specifically, the zebrafish is being exploited as a disease model to understand the mechanisms of COVID-19. Angiotensin-converting-enzyme-2 (ACE2) is an important protein in the renin-angiotensin-aldosterone system (RAAS) pathway. ACE2 is the receptor SARS-CoV-2 targets to enter and infect human cells. Kim et al.[19] studied the effect of RAAS inhibitors (aliskiren, olmesartan and captopril) on ACE2 expression in various organs of the zebrafish. They found that ACE2 expression is organ-specific and thus the benefit-risk analysis of using RAAS inhibitors in COVID-19 should be thoroughly investigated. Costa et al[20] also used zebrafish to study anosmia in Covid-19 and confirmed that the virus attacks the olfactory cells.

Laboratory Mouse (*Mus musculus*)

The disease models mentioned so far have their limitations because of differences in physiology and anatomy when compared to humans. This warrants the use of mammalian models for preclinical testing. Testing in mammalian models like the mouse also ascertains the pharmacodynamics and the pharmacokinetics of potential drugs that have been fished out using the other models. Still, it must be said that the experimental response in mice can differ from that in humans. For example, many cancer treatments that cure mice often have inadequate effect in humans and many prospective candidates never make it to the market. Nonetheless, the mouse is a relatively reliable model for humans and its genome is about 85% identical to the human genome.

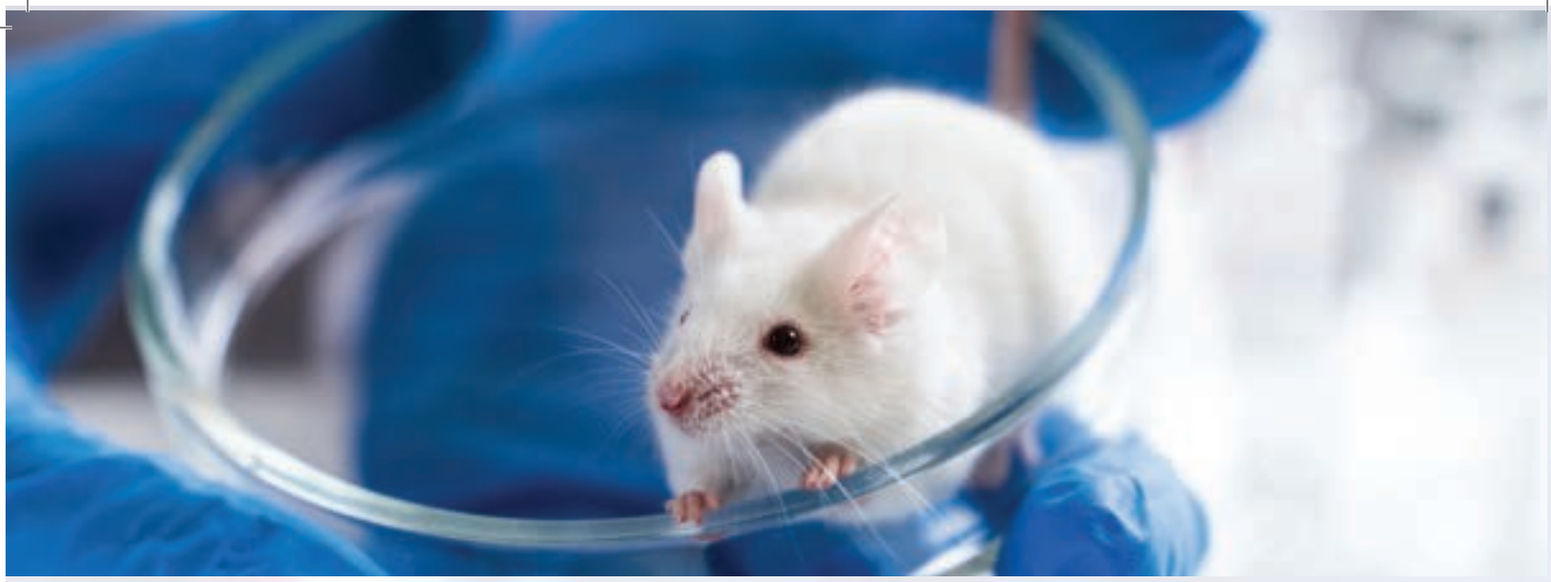


Table 5. Nobel Prize laureates and their contribution.

Year	Nobel Laureate	Contribution
2018	Tasaku Honjo James P. Allison	Cancer therapy (inhibition of negative immune regulation)
2016	Yoshinori Ohsumi	Autophagy mechanisms
2012	John B. Gurdon Shinya Yamanaka	Reprogramming mature cells to become pluripotent
2008	Harald zur Hausen	Human papilloma causing cancer of the cervix
1997	Stanley B. Prusiner	Prions discovery
1988	Gertrude B. Elion James W. Black	Principles for drug treatment

Breakthroughs using the laboratory mouse have netted about 17 Nobel Prizes. Table 5 shows the year and some of the names of the noble laureates who won a Nobel Prize. Again, this is a showcase of the biomedical research that has been vastly carried out using mice.

When it comes to behavioural studies, the laboratory mouse (*Mus musculus*) is one of the preferred models as it shares similar behavioural aspects with humans including sexual behaviour, anxiety, hunger, aggression, memory and circadian rhythm. There is also resemblance in anatomy, biochemistry, and molecular mechanisms. Over the years several mouse models have been created. Grayson et al.[21] used two such mouse models specifically to study schizophrenia, i) the 'prenatal restraint stress model' and ii) the 'chronic methionine mouse model'. They analysed the DNA methylation profiles in the adult offspring and found behavioural, epigenetic and other biochemical deficits. Such studies are providing solid evidence that early-life adversity and other environmental factors can mediate long-lasting epigenetic modifications in the brain, which are conducive to mental ill-health.

Using another mouse model Dr Yuan Shi and Mochen Cui et al.[22] found the underlying mechanism for the cognitive impairment and dementia associated with the long-term use of benzodiazepines. They found that there is loss of neuron connections. Specifically, they found loss of neuronal dendritic spines and synapse degradation, resulting from activation of microglia (immune cells of the central nervous system) which occurs when diazepam binds to TSPO (translocator protein), a protein on microglial organelles.

Winkler et al.[23] created a mouse model to study COVID-19 infection. As already pointed out, SARS-CoV-2 needs to bind to ACE2 receptors to infect the human cells. However, murine ACE2 receptor is structurally different from the human ACE2 and so Sars-CoV-2 cannot enter murine cells. Winkler et al. created a mouse that expresses human ACE2 in its epithelial cells. They then used this ACE2-transgenic mouse to model infection by SARS-CoV-2. They introduced the virus intranasally and found that the virus infected the lungs and then spread to other organs. Four days after infection, the lungs were compromised due to an infiltration with monocytes, neutrophils and activated T cells. They proposed that their mouse model could be used to further study COVID-19 infection and anti-viral treatments.

Further research by Tasuku Honjo and James Allison focused on apoptosis. They found that apoptotic T cells in mice that lacked an important receptor molecule, called 'programmed death molecule-1' (PD-1), go on to develop autoimmune diseases like type 1 diabetes, glomerulonephritis and myocarditis. PD-1 is an immune checkpoint protein and its upregulation leads to enhanced immuno-suppression. This research has paved the road to a promising new avenue for cancer immunotherapy through the use of checkpoint inhibitor drugs. Indeed, these drugs are offering hope in patients with advanced cancer. The cancers vary from advanced cutaneous squamous-cell carcinoma[24] to non-small-cell lung cancer.[25]

Cellular Models

A cell disease model can be a collection of cells derived from a tissue with a known disease. These cells are then cultured and researched *in vitro* to gain insights of the pathophysiological mechanisms specific to the disease. Such models are also being exploited to help discover molecular targets for treatment. They can also be used for testing out new treatments and thus help in developing new safer therapies.

Another type of cell disease model involves the use of induced pluripotent stem cells (iPS cells). For example, such cellular reprogramming platforms are offering insight in understanding neuropsychiatric disorders. In their review, Seshadri et al. [26] hypothesise that induced pluripotent stem cells (iPSCs) and their neural derivatives may be used to understand schizophrenia. Viswanath et al.[27] similarly reviewed cellular models to study bipolar disorders.

One important advantage of the traditional iPSC technology, when used to model human diseases, is that the induced cells have the whole genome of the donor and this makes it fit to dissect diseases caused by genetic errors. This platform is becoming more valuable when combined with CRISPR/Cas9 gene editing and genome-wide association studies. However, when it comes to studying epigenetics it faces a problem, namely that during the process of reprogramming, the epigenetic memory is erased (epigenetic erasure).[28] Thus mental illnesses that are epigenetically modified by environmental factors need to be studied by a sister technology called 'transdifferentiation' to generate functional-induced neurons (iNs).[29] Transdifferentiated cells seem to maintain the original epigenetic landscape.[30,31] However, such studies are still in their infancy.

CONCLUSION

The development of various translational disease models has been and still is vital to the comprehensive and expanding investigations into the diverse pathogenic mechanisms of disease and also, in bettering the identification of theranostic targets. The choice of the model employed is often a trade-off based on how much the disease model reflects and translates the human disease and on how easily the model platform can be manipulated. Surely, the integration of various advancing fields (like genomics, transcriptomics, proteomics, metabolomics and bioinformatics), together with automation technologies, when applied to such model organism systems, will enhance the discovery of biomarkers and of new and safer drugs.

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DR PIERRE VASSALLO

Breast Cancer Risk assessed by Mammography, US and MRI

INTRODUCTION

When looking at those factors that increase the risk for breast cancer, we find that there are specific factors that one can modify and others that are not modifiable.

Non-modifiable risk factors:

1. Female gender
2. Old age
3. Inheriting certain gene changes (such as BRCA1 and BRCA2)
4. Family or personal history of breast cancer
5. Race and ethnicity
6. Being taller
7. Having dense breasts
8. Having certain benign conditions e.g. atypical hyperplasia
9. Starting menstrual periods early or late menopause
10. Exposure to chest radiation
11. Exposure to DES (diethylstilbestrol) in utero.

Modifiable risk factors:

1. Drinking alcohol
2. Being overweight/obese
3. Not being physically active
4. Being nulliparous
5. Never breastfed
6. Hormonal contraception – very rare
7. Postmenopausal hormone therapy – rare
8. Breast Implant-Associated Anaplastic Large Cell Lymphoma – very rare

All these factors need to be considered when tailoring breast cancer screening programs to the patient's specific needs. They have been incorporated into the Tyrer-Cuzick Risk Calculator, which calculates the 10-year and lifetime risk score for developing breast cancer based on the above criteria.[1] The performance of these epidemiologically based risk models is improved by incorporating findings detected during breast imaging.

The primary aim of breast cancer screening studies is to detect breast cancer early to allow early treatment and improved treatment outcomes. However, they also have the potential to identify those individuals who are at increased risk of developing breast cancer.

This article describes the range of imaging features associated with breast cancer risk using digital mammography (DM), digital breast tomosynthesis (DBT or 3D mammography), breast ultrasound (breast US), and MRI.

IMAGING CRITERIA THAT INDICATE A HIGHER RISK OF BREAST CANCER

Breast density detected on mammography is an independent risk factor for breast cancer. Breast density is assessed on a four-category scale developed by the American College of Radiology (ACR). The scale forms part of the Breast Imaging Reporting and Data System (BI-RADS). Thus, individuals who have dense breasts on DM or DBT, have an increased risk for developing breast cancer.[2] In addition, dense breast tissue may obscure a cancer resulting in delayed diagnosis and potentially a poorer therapeutic outcome.[3]

Besides breast density, increased parenchymal complexity of the breast has been shown to correlate with a higher risk for cancer.[4]

Unlike mammography, breast US is capable of distinguishing glandular (ductal and lobular) from fibrous (stromal) elements of the breast. A higher glandular component that can be detected on breast US correlates with a higher incidence of breast cancer.

Finally, a higher background parenchymal contrast enhancement on breast MRI is also indicative of a higher breast cancer risk. Contrast enhanced mammography and molecular breast imaging are both capable of demonstrating background parenchymal enhancement. However, to date, these latter techniques are not widely used.

BREAST DENSITY ON MAMMOGRAPHY

Approximately 44% of women aged 20-74 have dense breasts.[5] The stromal (fibrous) and glandular components of the breast are the fibroglandular tissues that contribute towards breast density (whiteness) on DM and DBT. Adipose tissue is darker than fibroglandular tissue. Breast cancer most commonly occurs in the fibroglandular components. In addition, fibroglandular tissue may obscure breast cancer on mammography since both tissues have similar density.

Figure 1. BI-RADS classification of breast density is based on four categories that are assessed on medio-lateral oblique (MLO) mammograms:
A. Breast is almost entirely fatty.
B. Scattered areas of fibroglandular density.
C. Heterogeneously dense breast, which may obscure small cancers.
D. Extremely dense breast, which lowers sensitivity for detecting cancer.

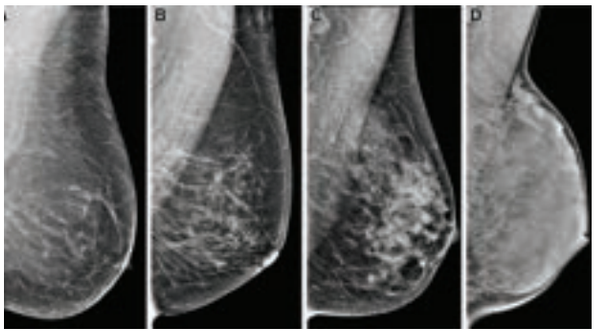
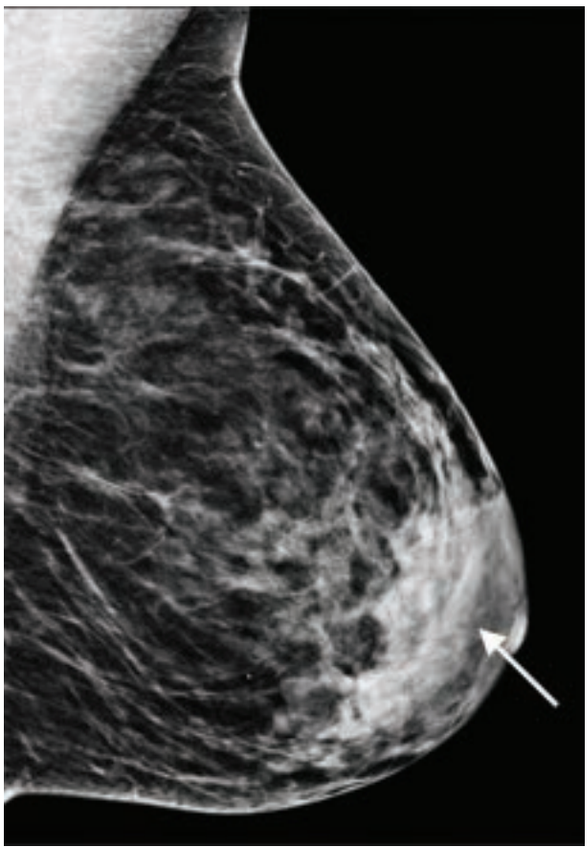


Figure 2. Note that the retroareolar density (arrow) shown in this left MLO mammogram could potentially obscure breast cancer. Therefore, even though most of the breast contains fatty tissue, this breast would still be classified as category C.



The BI-RADS classification method for breast density is based on a scale of four categories (Fig 1). Note that the classification is not based on the size of the area of increased density. It is based on the likelihood that the dense tissue might obscure a cancer (Fig 2).

Considerable inter-reader variability has been shown when using BI-RADS breast density assessment.[6] Several research groups have consequently attempted to use deep learning to mitigate this issue. There are currently at least nine U.S. Food and Drug Administration approved breast density assessment methods for DM, DBT and synthetic mammography (SM) using artificial intelligence.[7]

Using DBT, breast density can be assessed three-dimensionally in two ways: either as total dense breast volume or by measuring dense breast as a percentage total breast volume. Volumetric percental density has been shown to be more accurate for predicting breast cancer risk.[8]

BREAST PARENCHYMAL COMPLEXITY ON MAMMOGRAMS

Breast parenchymal complexity that is evident on mammograms can be quantified using computer analytical methods. Radiomic features are extracted using computer analysis of DM and can be displayed as heat maps[9] (Fig 3).

Figure 3. Radiomic analysis of the complexity of breast parenchymal texture that is then displayed in heat maps. The skewness map (A) shows the difference in textural complexity between one area and that adjacent to it, while the entropy map (b) shows the extent of disorder within the tissues. Red areas are those with high complexity and high disorder levels, while blue areas correlate with low complexity and low disorder levels.

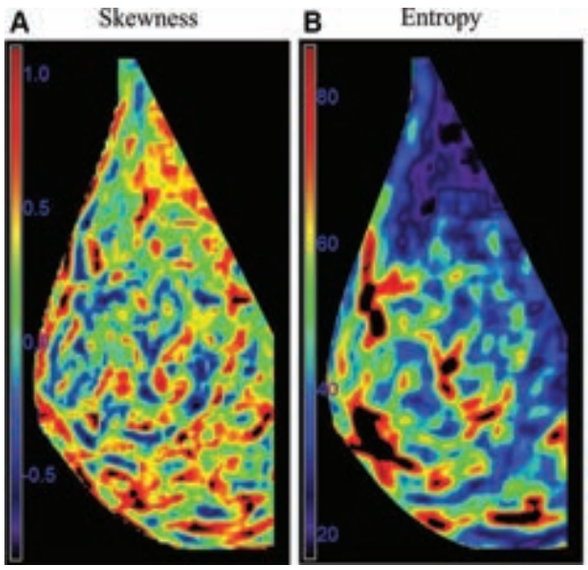
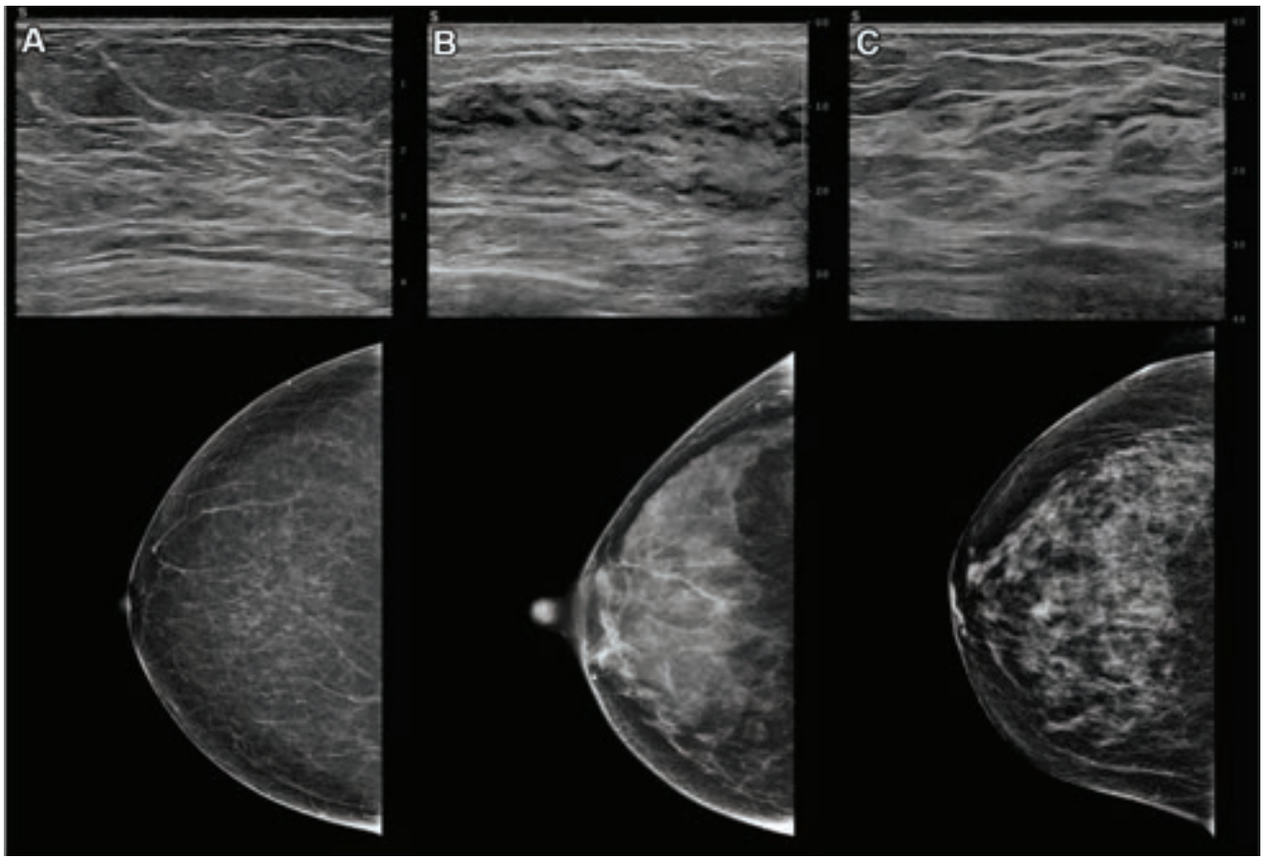


Figure 4. A. US category homogeneous background (fat) correlates with a fatty breast on mammography. B. US category homogeneous background (fibroglandular) corresponds to a dense breast. C. US category heterogeneous background correlates with a scattered fibroglandular elements on mammography.



Similar to increased breast density, increased parenchymal complexity is also associated with an increased risk for breast cancer.[4]

DEEP LEARNING IN BREAST CANCER RISK ASSESSMENT

Recent advances in deep learning have resulted in the computer being able to "learn" the features associated with cancer risk.[6]

Early studies that compared the results from the Tyrer-Cuzick calculator alone, DM features alone, and a deep learning model combining Tyrer-Cuzick and DM features, showed that the deep learning model delivered higher accuracy for diagnosing breast cancer. The same research group subsequently developed a mammography-based deep learning model that delivered an accuracy that surpassed the earlier one.[10] This is probably due to the improvement of deep learning technology with time and training.

One research group obtained the highest accuracy achieved so far by combining deep learning features (density, calcifications, masses) with familial, demographic, lifestyle, and polygenic risk scores that surpassed the Tyrer-Cuzick risk model.[11]

BREAST US

As discussed, the BI-RADS classification method for breast density is based on a scale of four categories (Fig 1). On the other hand, tissue composition on US is classified into three categories according to the BI-RADs classification: Homogeneous background (Fat), homogeneous background (fibroglandular), and heterogeneous background which is a combination of both fat and fibroglandular tissue (Fig 4). These categories correspond loosely with the four categories seen on mammography. Breast US can further distinguish stromal from glandular tissue within the

fibroglandular components of the breast; a higher proportion of glandular elements reflects a higher risk for breast cancer.

Internal echogenicity patterns of fibroglandular tissue on breast US may contribute to cancer risk assessment. However, standardisation of methods of evaluation and quantification as well as deep learning models will be required to develop a robust assessment method. In keeping with this, an international study that will evaluate the implications of sonographic glandular features on breast cancer risk is currently recruiting patients [ClinicalTrials.gov Identifier: NCT05460975].

BREAST MRI

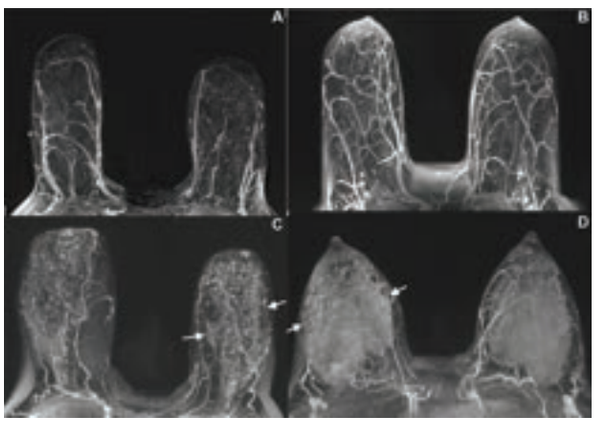
MRI is the most sensitive imaging modality for detecting breast cancer. Breast MRI features may be used to evaluate breast cancer risk.

Fibroglandular tissue is enhanced after administration of gadolinium-based contrast material; this enhancement is known as background parenchymal enhancement (BPE). BPE parallels the breast density categories seen on mammography: almost entirely fat, scattered fibroglandular elements, heterogeneous fibroglandular tissue, and extreme fibroglandular tissue (Fig 5).

BPE can be assessed visually (qualitatively) or using software (quantitatively). BPE is an independent risk factor for breast cancer, with high degrees of enhancement corresponding to a higher risk.

It is uncertain whether the degree of BPE is due to hormonal stimulation or glandular proliferation. Women with dense breasts who show a low BPE do not have a higher risk for breast cancer.[12] On the other hand BRCA1 and BRCA2 variant carriers who have had risk-reducing salpingo-oophorectomy, but in whom BPE remains high, still have an increased breast cancer risk.[13]

Figure 5. Qualitative BPE assessment according to the BI-RADS lexicon. Axial subtracted postcontrast, maximum intensity projection images of four different patients showing (A) minimal, (B) mild, (C) moderate, and (D) marked BPE (arrows).



Further evaluation of BPE for breast cancer risk prediction is required with the development of reproducible prediction models including deep learning models.

CONCLUSION

In addition to mammographic density, the above article describes a number of breast cancer risk assessment techniques which have shown promising results. However, these technologies require further evaluation and validation based on large prospective multinational studies. The ultimate goal is to deliver a tailored breast cancer screening strategy that is based on the level of breast cancer risk.

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