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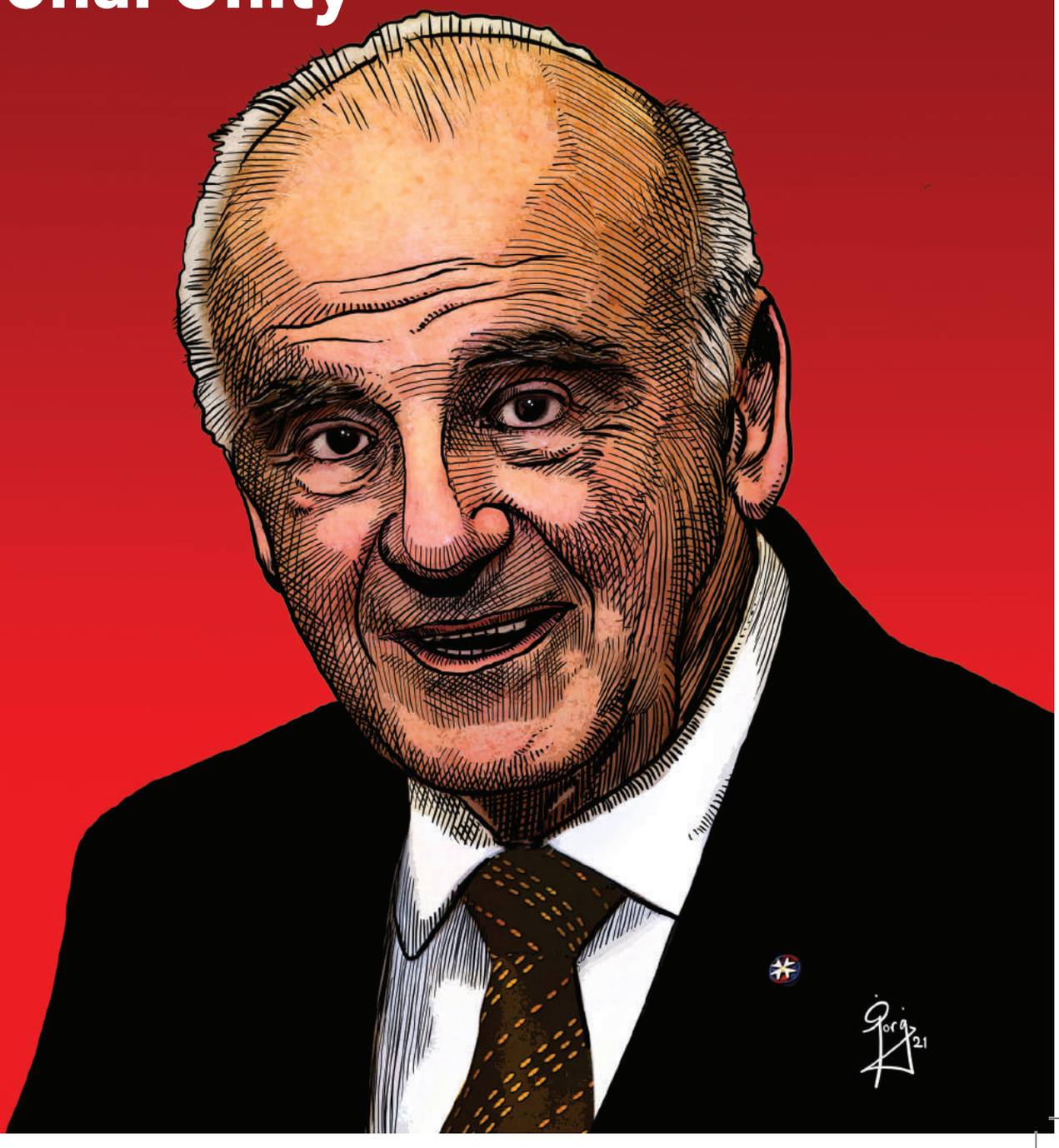
thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

The Synapse Magazine is celebrating its

20th Anniversary

The Need for **National Unity**



ENTRESTO® (sacubitril/valsartan) **Presentation**: Each film-coated tabletof Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Indications:** In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration:**The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **Contraindications**: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions**: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. 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. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in 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/valsartanis recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation . 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/valsartanimmediately 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 prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (ChildPugh 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. **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/valsartanis 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. Interactions between sacubitril/valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of 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, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Packs sizes**: Entresto 24 mg/26 mg–x28 tablets; Entresto49 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. 2020-MT-ENT-25-JUN-2020

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Issue Guide

TheSynapse

Front cover:
HE Dr George Vella, President of the Republic of Malta. Read the interview on page 5.
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MPSA

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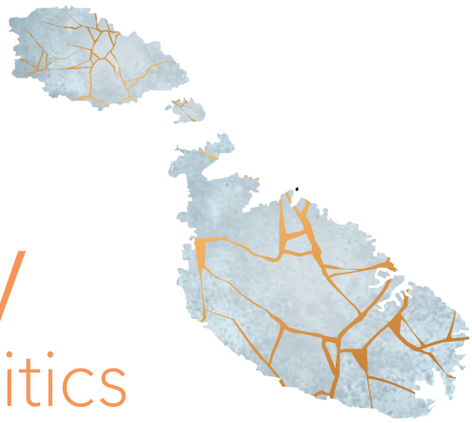
EDITORIAL



National Unity
Kintsugi VS Granular Politics

The General Election is beckoning, with important variants of SARS-CoV-2 serving as backdrop. In keeping with this, for this issue I considered it opportune to interview HE Dr George Vella, the President of the Republic of Malta. This, for two reasons.

The first point may be aptly illustrated by an excerpt from Woody Allen's 1977 romantic-comedy movie, *Annie Hall*. Two elderly women are at a mountain resort, and one of them says, "… the food at this place is really terrible." The other one replies, "Yeah, I know; and such small portions." How can one complain about the food but want a bigger portion?

In my opinion, such dichotomy, regretfully characterises our endemic parochial mentality, which we have all experienced since we were very young. A fitting example is the *festa partiti*. The latter has been meticulously detailed by the Dutch anthropologist Prof. Jeremy Boissevain back in 1964.[1] The upcoming election will invariably add its fair share of national acrimony due to the polarization which exists in relation to the main political parties; apart from partisan divisions, of course.

This attitude means that when one's tunnel vision is effectively translated into actions, this may cause conflict and consequentially, harm, whether intended or not. It thus seems that national unity is a can which has repeatedly been kicked down the road for several decades.

In my opinion, through his regular interventions on the matter, HE Dr Vella seems to epitomize a nation's overdue struggle for unity. The President's Office's endeavours have been crystallized through the National Unity Conference held on 27 February 2021. The purpose of the event was to bring together civil society at large and possibly pin down the cornerstones of nationhood … strong political will, identification of mutual goals, and mutual respect. The decision to avoid inviting politicians is commendable. After all, one of the politician's principal duties is to listen. Period.

The second reason for including such interview is that HE Dr Vella experienced the twin peaks of politics and medicine, being a hardened politician and also, a seasoned family doctor. This is of particular relevance in today's world, which is challenged and equally overshadowed by COVID-19. Indeed, politics and public health are known to be terrible bedfellows. Nonetheless during these past twelve months we have experienced a unique balancing act aimed at reconciling these seemingly dichotomous fields.

It is way too easy to criticize any decisions taken by the government to surf the pandemic waves amidst the different variants which are sprouting in different regions in the world. Here, we are still experiencing the influence of social media and the rifts which it can generate.

The President's Office has an important role to play since HE Dr Vella's political acumen offers a valid tool in the art of kintsugi. Again here, the strife for national unity should serve as antidote for the puerile tit-for-tat attitudes of the main political parties. The perceived management of COVID-19, including obviously enforcement, at a national level has not helped at all, with all its subtle percolations.

Then there is also Malta's post-COVID recovery, where we will all cross the river by feeling the stones. Nonetheless, it is utterly useless for the government to have a post-COVID strategy but then stop short of collaborating with champions such as worker union leaders, within health and beyond. Of note here are the numerous industrial actions which have been initiated, with some still ongoing, within the health sector by the various unions.

It is a shame that these industrial actions within the health sector have been craftily kindled and incessantly bellowed during the pandemic. I ask, who is to blame? The various healthcare professional sectors by any presumptuous demands? Or the government by its inherent inertia on specific issues? Can, however, the blame rest on specific union leader zealots? In reality, I do not know; possibly it is a cornucopia of these and many other issues which I cannot comprehend. What I do know, however, is that it is way too easy to pass the buck around. In my opinion this clearly shows how easy it is for key opinion leaders to rise in profile to the detriment of one's gravity. Sadly, it is the patient who ultimately suffers the brunt of our actions as healthcare professionals.

As you know very well, there is no yellow-brick road to national unity, Mr President … believe me, I do not envy your position.

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20th Anniversary

TheSynapse meets
H.E. the President of Malta

HE Dr George Vella, President of the Republic of Malta, can be described as a seasoned family doctor, a hardened politician, or simply, as an inspirational statesman. He accompanies Dr Ian Ellul down the memory lane, walking through his childhood, how he managed to enroll at the medical school, his work including his early years at the Drydocks, as well as the political turmoil of the eighties.

The interview also touches on the notion of GDP as an economic measurement tool, as well as national unity. Dr Vella possibly perceives national unity as kintsugi, the Japanese art in which broken ceramics are meticulously mended with a lacquer resin mixed with gold or silver, turning them into magnificent pieces of art.

YOU WERE BORN IN ŻEJTUN DURING WWII AND GREW UP IN ITS AFTERMATH. WHAT ARE YOUR CHILDHOOD MEMORIES?

I was born in April 1942, a month which demarcated Malta's heaviest bombardment in any given period. Fifteen days later, an anti-personnel bomb fell in the village's main square, leaving 27 dead and many injured.

I spent most of the childhood at my grandparents' house, also in Żejtun. The toys were rudimentary at that time. Street games included 'iċ-ċirku', 'noli', 'gwerra franċiża' and 'il-karretta'. However, my parents did not let me or my siblings, Violet and Freddie, to participate in street games. Fortunately, what was missed outside was aptly compensated by what was found inside; my grandparents lived adjacent to the Domus. The Domus lent itself as youth club, providing a large courtyard which served as playing ground, and it also housed theatrical performances, catechism lessons, mass and other events.

The highlight of our week was Sunday, when after lunch, our parents would take us for a walk in the countryside just outside the village. I still remember the sandwiches which my mother used to make. When my father eventually bought a car we used to go further out from Żejtun.

There were no TV, washing machines or fridges; poverty and social unrest were seen and perceived everywhere, stemming from the uncertainties faced by industry in post-war Malta. In Żejtun the majority of people, besides farming, worked at the Drydocks, including my father Emmanuel, and the future seemed bleak. This paved the way for mass migration. At one stage even my father had applied to go to Canberra in Australia; nonetheless, my mother Mary, on her mother's insistence, eventually convinced him to forget about migration.

Growing up, my mother missed on school since she was the eldest and had to help take care of her four siblings. However, eventually she was self-taught. Being an avid reader, books were all over the house; she even wrote poems and scripts for theatrical performances. As a consequence she had all eyes on us to ensure that we perform well in our studies. After primary education I attended De La Salle College. I have fond recollections of that period since the core values passed on to us were ingrained in the ethos of the school.

The Rediffusion radio broadcasting played an important role in Maltese culture. It consisted of two channels, channel A and B, transmitting in English and Maltese languages. Programmes related to music, literature, comedy sketches, especially by Radju Muskettieri, as well as serials including 'Ħitan tas-Sejjieħ' and 'Il-Farfett l-Aħdar'. Everyone used to hear them. I still vividly remember walking to my grandparents' house in Summer and listening to entire comedy sketches of the Stage Commandos as I walked down the street, with the same voices bellowing out through the open windows of the different houses.

At 14 years of age, in 1956, Malta experienced the advent of television which heralded a silent revolution which percolated through all societal strata. At the beginning, those few houses which had a TV had to keep up with the neighbours who used to self-invite themselves to watch the local news and other programmes.

The TV obviously had an impact on fashion, football, Italian songs, etc. Of note is the fact that it led to an uglification of the environment in Malta, with the 'afforestation' of rooftops with antennas that were needed for receiving TV signals.

WHY DID YOU CHOOSE TO BECOME A DOCTOR?

I was neither exposed to anything like today's numerous TV series relating to hospital practice nor did I have relatives who were medics. I believe that my interest in medicine must have stemmed from Dr George Hyzler. He was a friend of my uncle and used to call regularly at my grandmother during his undergraduate years at the medical school, where he used to sometimes bring a human bone or two and show them to me. (His son, named after him, would eventually also enter politics and currently serves as Commissioner for Standards in Public Life). My interest in medicine however, abated over the years.

At that time De La Salle did not have a 6th form and University used to open courses in Medicine every two or three years. It was also a period when the majority of students opted for an executive officer job with the government; however, after finishing secondary school in 1956, I decided to further my studies. A friend advised me to seek guidance from Mr Glass, headmaster of the Valletta Lyceum to enter their Sixth Form. Mr Glass informed me that I had to sit for 13 exams to enroll at Sixth Form, and I reiterated that, in that case, I might as well do the Matriculation exams on my own. His reply still echoes in my head … 'Some people do think highly of themselves.' That meeting proved to be a watershed moment. I decided to sit for the Matriculation exam on my own steam.

A few weeks after, I also visited Laurence Pace who was the registrar at the University, in Valletta, to seek advice with regards to my possible enrollment in the medicine course. He bluntly pointed out that I did not have any Biology, Chemistry or Physics exam certificates. Nonetheless, I still remember his words of encouragement; he proposed that I study Additional Mathematics since it equated to a science subject. Thus I studied for the Matriculation exams, including the Additional Mathematics, whilst working as supply teacher at De La Salle.

During that summer of 1957 I also remember speaking to Prof. Edwin Borg Costanzi, who was the Rector of the University, asking what would become of me if I failed the Additional Mathematics exam coming up in September. I was worried, of course, since choosing to study at the University was pricy. The fee amounted to around 54 Maltese Lira for one academic year. (In 1960 the fees doubled which led to various student protests). Returning to Prof. Borg Costanzi I remember him saying that failing the Additional Mathematics exam would mean forfeiting my enrollment in the medical course. This fuelled my motivation to pass. Indeed, I successfully obtaining all exams and started studying medicine in 1957.

I HEARD YOUR NAME FOR THE FIRST TIME THROUGH MY FATHER WHO USED TO WORK AT THE DRYDOCKS. YOU GRADUATED AS DOCTOR IN 1964 AND AFTER YOUR HOUSEMANSHIP PERIOD ENDED, YOU STARTED TO WORK AT THE DRYDOCKS TILL 1974. WHAT DO YOU RECALL FROM THIS EVENTFUL PERIOD, ALSO GETTING MARRIED AND HAVING YOUR THREE CHILDREN?

During my two years working at St Luke's Hospital I decided that I would specialize in industrial medicine at the University of London. However, chance has it that my brother asked me whether I was interested to work at the Drydocks to relieve the resident medic. So I started as a locum there while I was also working as physiology demonstrator at the University. I was getting married soon. Eventually I was offered a part-time job at the Drydocks with an annual salary to the tune of 1000 Maltese Lira which was enticing, to say the least; in comparison, a seasoned District Medical Officer used to earn 800 Maltese Lira. I accepted the job, keeping my budding practice as family doctor in Żejtun and also, working as company doctor in industry and various hotels, including the Sheraton [in place of the Westin Dragonara Hotel]. In the meantime, I still aspired to specialize in industrial medicine.

As it happened, one fine night I was called to assist a cyanotic patient suffering from wheezing. With a young racing heart, expecting the unexpected, I arrived in the Biskallin area of Żejtun [known as 'ir-Raħal t'isfel'] where I found scores of people waiting for me outside the patient's door. After gauging the situation, I started the process of administering IV aminophylline, a relatively new treatment … explaining what needs to be done to the numerous relatives, addressing their doubts, then pulling out the syringe, hearing murmurs in the background, administering the treatment slowly over 15 minutes whilst addressing again their loud thoughts, and … hoping for the best. Thankfully, everything went exceptionally well. The patient even recovered his strength and accompanied me to the door. This proved to be an unexpected boost to my practice, which was to be followed shortly by another unrelated event which affected my fortunes.

Dr John Borg, a very popular and much loved doctor in Żejtun died unexpectedly. This meant that his patients started calling me to become their family doctor. The result was that my aspiration to specialize in industrial medicine had to be shelved [to this very day] and my employments with the Drydocks and University terminated to work as a full-time family doctor.

ANY EVENTS YOU REMEMBER IN PARTICULAR AT THE DRYDOCKS?

In the sixties the Drydocks were synonymous with hardships and occupational hazards which were often disregarded. Safety measures, considered as ubiquitous today, were unheard of … no safety shoes or helmets, no fume extractors, etc. I came at loggerheads with management regularly on such issues.

I remember visiting Manoel Island where workers used to produce Melita fiberglass boats. As expected, there were no fume extractors, no safety helmets, no safety flooring, etc. After I stopped all work in the huts [until the safety issues were addressed], Major Stanley Clews, who was in charge of personnel at the Drydocks, called me in his office and asked me whether I was employed with the Drydocks or the workers. I simply reiterated that my duty was to safeguard the work conditions of all employees while being paid by the Drydocks. This informal meeting was followed by numerous reports from my end soliciting for the introduction of safety gear for the 5,300 workers who worked at the Drydocks at that time.

Numerous memories relating to occupational incidents come my mind. We used to have workers getting injured from falls, fires, etc. When shifts were introduced this heralded a new set of problems … headaches, vomiting, vertigo. Obviously, people used to visit me to discuss their personal problems, including job insecurity and salary issues.

I must admit that the most harrowing memory is that of a naval vessel which, in 1967 during the Six-Day Middle-East war, was caught in friendly bombardment resulting in 15 dead soldiers entrapped in the entangled metal of the bow. This Israeli ship came to the Drydocks to be cleaned and repaired. Awnings had to be set up to avoid inquisitive eyes from Senglea's bastions. I remember water being pumped from one side of the bow to cleanse the area, with blood-tainted water gushing out from the other side.

Another seemingly minor incident had dire consequences. A worker was on staging inspecting the shaft of the propellor of a tanker which was removed for repairs. As he was gauging the alignment of the shaft, his wedding ring [which shouldn't have been worn] was caught in the shaft's slow rotatory movement, was lifted bodily and his head struck the strut. Following that event the worker started suffering from regular fits, headaches, and recurrent bouts of feeling unwell until he retired.

An amusing incident happened at the beginning of my career. The captain of a ship had a dislocated shoulder on deck and I advised him to go to St Luke's Hospital. He vehemently refused and bravely insisted I put the humerus back in place. To keep up appearances, I accepted to do so, obviously advising him that it would incur great pain. Being the first time I ever did this textbook manoeuvre, I thoughtfully removed my shoe, cautiously placed my foot in his axilla and pulled! Thankfully all went well.

I also want to mention another accident. Back then when work was required in the bow of a ship, especially tankers, workers had to descend from the middle of a vessel to walk approximately 150 metres through the bilges to reach the front part of the vessel. It so happened that during one such repair, a fire developed between the bow and the entry point. Fortunately, the fire was extinguished with minor consequences to the workers. In the management meeting which followed I proposed that a manhole is cut in the bow whenever such works are required, to serve as emergency exit in case of fires. As a young doctor I was derided, of course. Two months later, precisely on a Saturday, I was called in because of a fire on a tanker. I arrived there and saw people gathered around the bow. On my arrival I was informed that for the first time they fortuitously followed my advice of drilling a manhole in the bow! Fifty workers were saved by that small action that day. This safety measure is still being done to this very day.

HOW DID YOU PERCEIVE THE CHANGES IN THE FIELD OF FAMILY MEDICINE DURING THESE PAST FIVE DECADES?

The practice of medicine has made quantum leaps. In my opinion, this can be primarily attributed to technology. Let me give an example. It was the seventies and a twelve-year old girl suffered an injury, with a pair of scissors penetrating the sternum and causing pericardial injury. Prof. Victor Griffiths operated her and

a continuous ECG was required, something we had not seen before. Getting an ECG done meant submitting a formal request for the ECG to an ECG technician, wait for your turn and then wait for its arrival.

When I graduated there was no ultrasound so, in obstetrics, one had to have good semiotics to try to guess whether the mother was having one or more babies, figure out the position, etc. In keeping with this we were heavily assessed on auscultation skills during our undergraduate years. Cardiology interventions being performed locally, on the other hand, were basic, if any. The first time I experienced open heart surgery [for aortic stenosis] was in 1962 during my surgery clerkship in Berlin. I remember coming back and being asked by Prof. Joseph Zammit Maempel to recount the procedure.

Of note is the introduction of fibre optics which heralded a new era in endoscopy. Prior to this, doctors could only use rigid straight tubes, which were of course, inadequate, uncomfortable and gave limited information.

YOUR CHILDREN, GEORGE JR, CLAIRE AND ELAINE, DID NOT FOLLOW YOUR STEPS. IT SEEMS THAT THIS HAS BEEN APTLY COMPENSATED BY YOUR GRANDCHILDREN.

I guess my work-life balance deterred my children from choosing medicine. I worked from Monday till Sunday, regularly clocking up to 80 hours weekly. Doing urgent home visits up to three nights a week was common practice. In those times there were no polyclinics and frequently, patients refused to go to St Luke's. This meant that I had to treat them to the best of my knowledge [and hope for the best]; treating three heart failures in one night with digoxin and strophantin together with morphine was not a rare event. Although the work brought food to my table, together with social respect, this meant that the upbringing of my children rested entirely in the caring hands of my wife. Eventually I came to realize that this was not sustainable, so I decided to stop my clinic early Saturday afternoon to dedicate more time to my family.

Skipping a generation, three out of my seven grandchildren are now enrolled in medicine. George's daughter is in 4th year whilst the daughters of Elaine and Claire are both in 2nd year. Although I tried to avoid influencing them, I am obviously pleased that they are following my steps.

WHAT WOULD BE YOUR MOST IMPORTANT SINGLE PIECE OF ADVICE TO YOUR GRANDCHILDREN?

Malta has progressed considerably when compared to years past, with social justice now ingrained in our culture. I strongly believe that specific values constitute the foundations of an orderly society and these do not age with time. They include honesty, transparency, accountability, speaking the truth and doing what is right. Living these values means that when one grows old and looks back, one can peacefully state that any past deeds have been done with good intentions.

MOVING ON TO POLITICS, DO YOU IDENTIFY YOURSELF WITH CONSERVATIVE SOCIALISM?

Socialism does not equate to conservatism. Traditionally, conservative policies have been invariably associated with the Nationalist party; socialism, on the other hand, identified itself mostly with blue collars. Socialism is progressive, at times slightly revolutionary in a pacific sense.

Socialism is built on the foundations of labour which is the workers' movement lobbying for right to work, decent salary, and right to enroll in unions. Socialism, on the other hand, relates more to camaraderie, with workers contributing to assist disadvantaged and disabled colleagues. This includes paying taxes to subsidize housing projects, social services, etc. Needless to say, all this should be distinguished from extreme socialism which is, in fact, communism.

Socialism was seeded in me by my working class family and nurtured by living in post-war Malta. When I stepped in the Drydocks I felt inherently obliged to advocate the rights and well-being of the workers, penning various articles in local newspapers, challenging the pernicious perception that Drydocks workers were social loafers.

As time passed by, socialism became infiltrated by more liberal ideas. How can I not endorse specific changes in civil liberties, including LGBTI rights? However, euthanasia and abortion, portrayed as being 'liberal' measures by socialists, are a different story. I strongly believe that core values stem from life, rather than politics. In keeping with this, prior to accepting my current position I was clear that I will never sign any legislation relating to the introduction of euthanasia or abortion in Malta.

WHAT MOTIVATED YOU TO RUN AS A LABOUR PARTY CANDIDATE ON THE 3RD DISTRICT BACK IN 1976?

Back in the seventies, all political parties turned to doctors since they were considered knowledgeable on the general electorate sentiment. At that time up to 25% of MPs were doctors. By 1974 I was a young family man with a working class background; this, together with my expanding medical practice and my experience at the Drydocks seemed to tick all the right boxes for my candidature. Notwithstanding this, I resisted all attempts

I SUDDENLY HAD TO FACE UNEXPECTED CONSTITUTIONAL CHALLENGES WHICH POSED KNOTTY LEGAL CHALLENGES DUE TO DIFFERENT INTERPRETATIONS BY LEGAL EXPERTS. THESE RANGED FROM REQUESTS FOR THE REMOVAL OF A PRIME MINISTER FROM OFFICE AND TO CHANGE THE LEADER OF THE OPPOSITION, TO PRESIDENTIAL PARDONS

to run for election. Actually, Wistin Abela used to tell me that he was constrained to run for election on the 3rd district because I did not want to do so!

One day as I was in St Thomas Bay in Marsascala someone came along congratulating me for accepting to run for the 1976 election. Upon enquiring, he informed me that Lorry Sant had declared so, earlier on, in a meeting in Tarxien. The rest is history. I did not get elected in 1976 but when Emmanuel Attard Bezzina resigned from parliament to take up the role of Maltese Ambassador to Germany, I was co-opted on 16 January 1978.

AS MINISTER YOU WERE ALWAYS ASSIGNED FOREIGN AFFAIRS. WHY WERE YOU ALSO HANDED THE ENVIRONMENT BETWEEN 1996 AND 1998?

After being co-opted in 1978 Dom Mintoff asked me to attend the Conference of Local and Regional Authorities in the Council of Europe on matters relating to neighbourhood councils with the intention to implement a similar system in Malta. [This concept eventually led to the introduction of local councils]. At the Council of Europe I was then asked to choose a working group and I opted for the Committee of the Environment. There I was appointed rapporteur on maritime pollution from maritime sources [oil transportation at sea, maritime disasters including oil spills, etc].

The Council of Europe is a steep learning curve since it provides a cornucopia of subjects, opinions and countries. I strongly advice all prospective electoral candidates to work there for some time if the occasion arises. My experience there in both foreign policy as well as environmental matters motivated Dr Alfred Sant to assign me a Ministerial portfolio including both, after the Labour Party won the election in 1996.

ANY ANECDOTE DURING YOUR POLITICAL CAREER?

Parliamentary life has its share of satisfaction which more than compensates the sacrifices which one makes, including any income lost from one's private practice in order to attend parliamentary sessions, attend meetings abroad, etc. Indeed, the balancing act on the twin peaks of politics and family medicine created opportunities for me to voice the concerns of patients in the corridors of the highest governmental institution.

Unfortunately, sad recollections also come to mind. Political acrimony and indiscipline crystallized the seventies and eighties. The murder of Karen Grech in 1977, the Żejtun tal-Barrani march in November 1986 and the ensuing murder of Raymond Caruana in Gudja epitomises that era.

The 1977 medical strike at St Luke's Hospital was a thorny issue. How can one run a national hospital without any doctors? I volunteered to close my clinic to go and work there. Doctors working at St. Luke's had to be very careful since the government was ready to declare a state of emergency and coerce specific surgeons to return to work, if need be. If an acute abdomen presented itself at St. Luke's, did it warrant surgery? What if we requested surgery in an erroneous manner and a state of emergency was invocated in vain? I also remember going around St Luke's at night switching the lights to allay patients' concerns that there were no doctors; in reality there were very few.

I still believe that the medical strike was heavily politicized. Because of the strike though, for the first time, medical doctors arrived from countries other than the UK, including Algerian, Egyptian, Belgian and Yugoslav specialists, to bolster our ailing efforts. This led to an influx of foreign expertise which Malta lacked. Obviously, after the strike ended, strike-breakers, including myself, suffered the brunt of social boycott by medical consultants for a number of years.

The 1981 elections which followed constituted a watershed moment. The Nationalist party got the absolute majority of votes, but a minority of parliamentary seats. This created a political conundrum. Dom Mintoff formed a government, as he was constitutionally obliged to do. I remember going to the Council of Europe together with Dr Joe Buttigieg and Leo Brincat to defend our case and explain that we were constitutionally correct. Dom Mintoff, in an attempt to cross the river by feeling the stones, started a reform process from both sides of the House to correct this anomaly and made it clear to us MPs that the following year he would call fresh elections.

In 1982 the agreement to call another election faced strong opposition from the parliamentary group. In view of this, Mintoff felt that his only way out was to resign from Prime Minister and party leader. This he did in 1984, but not before appointing Dr Karmenu Mifsud Bonnici in his stead. He wisely decided to not appoint Lorry Sant or Lino Spiteri, since this would have retained the political inertia within the Labour party. With all his good will, Dr Mifsud Bonnici did not manage to clean the Augean stable; regretfully many people took advantage of his naiveness.

Following the Żejtun wedding incident involving Dr Eddie Fenech Adami in June 1989, Dr Wenzu Mintoff and Dr Toni Abela resigned from the Labour party in protest. The evening before their resignation they were at my house in Żejtun inviting me to join them. However, I had consistently made it clear that one can only advocate for change from within the party ranks. I recall challenging Dr Mifsud Bonnici, on what would happen if three incidents similar to the tal-Barrani incident would happen at the same time … a civil war would be on his hands. Although painstakingly slow, through a concerted effort from few willing people we managed to press forward important reforms such as the Commission for Discipline and Vigilance, Ethics Committee, etc.

IN 2017 YOU RETIRED FROM POLITICS. AFTER TWO YEARS DEDICATED TO YOUR FAVOURITE PAST-TIMES – PHILATELY, READING AND CLASSICAL MUSIC - YOU WERE INAUGURATED AS THE 10TH PRESIDENT OF MALTA IN APRIL 2019.

At 75 years of age I was becoming increasingly convinced that I should pack up and thus I decided to call it a day. This meant that I had ample time to dedicate to my hobbies. I read over 45 books in 2018 alone, mostly relating to history. My interest in history stemmed from a visit in 1960 to Florence when I came to realize that viewing renaissance sculptures without any knowledge of art or history, in reality meant nothing to me. Along the years this passion extended to history in general. However, if I were to recommend a specific book, I would mention the volumes of the Jesus of Nazareth series, penned by Pope Benedict XVI, relating to the last few days of Christ.

On the other hand, my passion for philately traces its roots to my childhood days. I would go to the Strand in London and buy stamps from shops there. I eventually branched to UK postal history, and eventually postal stationery. Today I have a good collection of Victorian postal stationery of 1837 – 1901, as well as postal stationary relating to various UK prime ministers.

I also love all types of classical music. I am not a cognoscente but when I was at my home in Żejtun, classical tunes were played in my study, changing accordingly to reflect my mood.

All this changed two years ago. Regretfully the pandemic has now redefined my day-to-day official activities, of course. I miss the official functions, as well as the community outreach which characterize the work of the Presidential Office.

THE PRESIDENT'S OFFICE IS INTRINSICALLY ASSOCIATED WITH CHARITY WORK. NONETHELESS, SINCE YOU TOOK OFFICE YOU HAVE BEEN ROPED IN ISSUES STEMMING FROM THE DAPHNE CARUANA GALIZIA SAGA [PRESIDENTIAL PARDONS, CIVIL SOCIETY PROTESTS, ETC] AS WELL AS ISSUES RELATING TO LEADERSHIP TURMOILS OF THE BOTH MAIN POLITICAL PARTIES. RECENTLY YOU QUOTED DUN KARM PSAILA'S WORDS, 'SEDDAQ IL-GĦAQDA U S-SLIEM'. WHY DO WE NEED NATIONAL UNITY?

I suddenly had to face unexpected constitutional challenges which posed knotty legal challenges due to different interpretations by legal experts. These ranged from requests for the removal of a Prime Minister from office and to change the leader of the Opposition, to presidential pardons. Although I am now a retired physician, I am still practicing those very same medical principles which have been ingrained in me over the years … listening without any prejudice and with an open mind, assimilating all information, making a differential diagnosis, gauging all possibilities and then acting.

The dichotomy of our small population is beguiling. There are way too many societal fractions which are present even at a local level, including band clubs, football clubs and political parties, of course. On the other hand, our society manages to unite on specific occasions e.g. national fund-raising activities, and facing the pandemic.

My role is to try to bridge unnecessary differences and push for awareness for the need of national unity. I need to respect you if I am willing to accept these differences. The things which we have in common must unite us. We have been kicking the can down the road for too long. I am referring here especially to the abuse we see on social media, including disrespectful communication and sheer insolence.

I intentionally did not invite politicians for the conference on National Unity held by my office a few weeks ago. I wanted to avoid partisan politics. However, I expect them to sit down and listen to the conference

proceedings relating to the entire spectrum of opinions of the civil society participating in the conference.

GEORGE VELLA AND FUNERALS WHAT IS THE RELATIONSHIP?

One of the most distressing life traumas was my attendance to a funeral of a fellow student when I was 14 years old. The grief and overwhelming emotions which I witnessed marked me for life and I decided to never attend funerals again. In 1973 I convinced myself to attend the funeral of Dr John Borg, mentioned earlier, but those very same emotions - experienced 17 years before – set in again and I had to leave early. This second lugubrious experience reinforced my conviction to never to attend funerals again. In fact, I did not attend my parents' funerals.

I admit that I never found any difficulties to make house visits to issue death certificates, but whenever the coffin arrives, uneasiness sets in. When it comes to state funerals, these are very different since they are more formal and less intimate; however, I try to avoid them as much as possible.

ACCORDING TO EUROSTAT, MALTA RECORDED THE 2ND HIGHEST GDP GROWTH AMONG EU STATES IN Q4 OF 2020. BETWEEN 2013 AND 2019 WE HEARD MUCH ON THE SINGAPORE GDP MODEL OF ECONOMIC PROGRESSION WHICH MALTA SEEMED TO ASPIRE TO EMULATE. DO YOU CONSIDER NEW ZEALAND TO USE A BETTER INDEX IN RELATION TO A NATION'S ECONOMIC WELLBEING?

I totally agree that the GDP must be superseded by other more granular economic tools to measure the wealth of a nation. Many other variables should be considered, including socio-economic issues including social justice; this includes violence on women and mistreatment of children. The environment including access to open spaces, is another important variable, which has a direct effect on mental well-being.

THE PRESIDENT'S OFFICE & SUSTAINABLE DEVELOPMENT GOALS?

My role is to actively promote the SDGs whenever possible. In reality, Malta has progressed markedly when it comes to education, civil rights, etc. The environment is especially important. Five SDGs relate specifically to the environment with the remaining SDGs referring indirectly to them. Similar to what has happened to their precursors, the Millennium Development Goals, I am convinced that the set target of 2030 will be extended again. In keeping with this, it is important to keep in mind that the achievement of these goals will not lead to a perfect world; rather, these goals serve to achieve a more sustainable future for all.

MAYBE IT IS TOO EARLY, BUT WHO WOULD YOU LIKE TO SEE AS THE 11TH PRESIDENT OF MALTA? A TECHNOCRAT? A MEMBER FROM THE OPPOSITION RANKS?

I do not believe that the chair of a President of Malta can be adequately filled by a technocrat. Political experience is of the utmost importance. If one interprets the constitution ad litteram from a legal point of view only, one may miss important political implications. One's political experience is worth one's weight in gold when occupying this position.

When I was approached for this position, I was reluctant at first. However, one then starts wondering whether they asked you because they see qualities in you which might make you fit for purpose. Logically, I cannot guess which person would be most fitting for this role in three years' time since I do not know what the circumstances of Malta will be in 2024. However, similar to what happened in my case, I strongly believe that a nomination for President should be agreed by both sides of parliament.

I can reassure you that whoever occupies this position manages to remove one's partisan cloak. I dedicated enough time and energy to partisan politics. I describe myself as a hardened politician with five decades experience as family doctor. In spite of this, it is still heart-wrenching for me to see all the Community Chest Fund's requests, especially those relating to young, severely ill, children.

EVERYONE HAS PERSONAL REGRETS. YOUR GREATEST ONE?

Leaving my private practice in 2013 left a void. At times, a previous patient of mine phones me for medical advice and something rekindles in me, making me yearn for those days when I was of service to my patients.

DESCRIBE YOUR LIFE IN ONE SENTENCE?

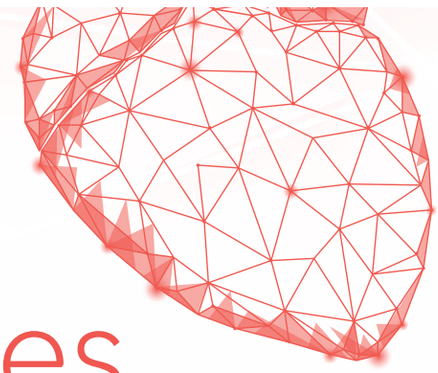
I thank God Almighty of all the gifts of life which I received from Him. I do not know whether I have deserved them all. Many other people may not have had my good fortune because of illness or family misfortunes ... I feel lucky.

WHY DO YOU READ THE SYNAPSE MAGAZINE?

I always eagerly await its arrival and read it from cover to cover. It keeps me updated on what is happening locally in the medical field including new technologies, interventions and treatments. Keep up the good work!

Editor's note: This interview is dedicated to my father, William Ellul, who worked at the Malta Drydocks for 47 years between 1953 and 2000.

DR TIZIANA FELICE



Inherited Cardiomyopathies and Genetics

ABSTRACT

Cardiomyopathies are a clinically heterogeneous group of cardiac muscle disorders. They are defined by the presence of abnormal myocardial structure in the absence of ischaemic and valvular heart disease, hypertension and congenital heart disease. There are five main types of inherited cardiomyopathies: hypertrophic, dilated, arrhythmogenic right ventricular cardiomyopathy, restrictive and left ventricular non-compaction cardiomyopathy. For most cardiomyopathies autosomal dominant transmission is the commonest mode of inheritance except for those caused by metabolic disorders. Cardiomyopathies are associated with the early development of heart failure and an increased risk of sudden cardiac death often claiming the lives of young patients. Advances in molecular genetics have allowed us to better understand these myocardial diseases allowing for better clinical diagnosis, management and familial screening. This review will focus on the genetics in HCM and DCM.

Key words: Hypertrophic cardiomyopathy, Dilated cardiomyopathy, Heart failure, Sarcomere, Genetics

INTRODUCTION

Cardiomyopathies are disorders causing abnormalities primarily in the structure and function of the heart in the absence of coronary artery disease, valvular heart disease and hypertension. These disorders are commonly grouped into morphological subtypes that include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and left ventricular non-compaction cardiomyopathy (LVNC).[1,2] Early clinical investigations showed familial transmission in individuals with cardiomyopathies suggesting a critical role for genetics. Research advances over the past thirty years confirmed this hypothesis and today many cardiomyopathies are recognized as monogenic disorders. Most cardiomyopathies are often inherited in an autosomal dominant manner. This literature review will focus on the genetics of HCM and DCM.

GENETICS IN HYPERTROPHIC CARDIOMYOPATHY

HCM is defined by the presence of increased left ventricular (LV) wall thickness that is not explained by abnormal loading conditions, such as hypertension.[3] An index case is diagnosed with HCM if the LV wall thickness is ≥ 15mm in one or more myocardial segments, whilst first-degree relatives are diagnosed with the condition if the LV wall thickness is ≥ 13mm.[3] The above definitions are in accordance with the 2014 European Society of Cardiology guidelines on the diagnosis and management of hypertrophic cardiomyopathy.

HCM is a monogenic disease caused by variants in genes that encode the protein components of the cardiac sarcomere. HCM is the commonest inherited cardiac disease with an incidence in the population of 1 in 500.[4] Therefore in Malta it is estimated that approximately 900 individuals will be affected with this condition. HCM is transmitted in an autosomal dominant manner and therefore first-degree relatives of affected individuals have a 50% chance of developing the disease. It is the

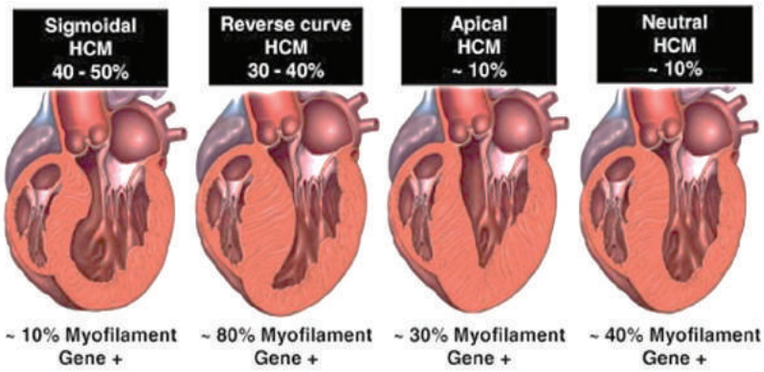


Figure 1. Septal Morphologies in HCM. Shown are the most common septal morphologies in HCM. The distribution of septal morphologies among a large cohort of patients with HCM is shown along the top while the yield of genetic testing for each morphological subgroup is shown along the bottom of the figure. Bos JM, et al. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. *J AM Coll Cardiol* 2009;54:201-211.

commonest cause of sudden cardiac death (SCD) in young athletes, and may also progress to heart failure.[4] Penetrance is often incomplete and individuals express the clinical phenotype later on in life, in adolescence or adulthood.[5] Identical HCM variants within the same family may result in varying degrees of disease phenotype and severity. The morphology of cardiac muscle affected with HCM is characterized by cardiac myocyte hypertrophy, myocyte disarray and increased myocardial fibrosis. The cardiac myocytes have distorted nuclei and disorganised myofibrils. These changes alone may lead to decreased cardiac relaxation, arrhythmias and progression to heart failure.[4] Figure 1 shows the different types of HCM depending on the location and morphology of the hypertrophied segment.

Individuals affected with HCM may have a variety of symptoms. They often complain of palpitations, chest pain or shortness of breath. Unheralded syncope may occur and this may precede sudden cardiac arrest as it is often caused by a malignant ventricular arrhythmia. Patients are more symptomatic in the presence of left ventricular out flow tract (LVOT) obstruction where they may develop chest pain, dyspnoea or dizziness on walking uphill or upstairs which are worse after eating a heavy meal. The management of patients with HCM involves treating symptoms and protecting patients from SCD. Drugs worsening the gradient across the LVOT should be withheld, such as ACE-inhibitors, nitrates, dihydropyridine calcium channel blockers and digoxin. LVOT obstruction is treated with beta-blockers, non-dihydropyridine calcium channel blockers or disopyramide. If symptoms persist surgical septal myectomy or alcohol septal ablation may be considered. A patient's risk for SCD is assessed using the European Society of Cardiology's HCM-SCD risk score and if the calculated risk is ≥ 6%, an implantable cardiac defibrillator will be inserted.[3] This risk score takes into consideration the maximal wall thickness, the left atrial diameter, the LVOT gradient, any family history of SCD in a first-degree relative age <45 years, the presence of non-sustained ventricular tachycardia on holter, and syncope.

The first identified HCM–causing mutation was discovered in 1990. Since then several studies have demonstrated disease-causing variants in eight genes: β-myosin heavy chain (*MYH7*),[6] α-tropomyosin (*TPM1*), cardiac troponin T (*TNNT2*),[7] cardiac myosin binding protein-C (*MYBPC3*),[8] myosin regularity light chain (*MYL2*), myosin essential light chain (*MYL3*),[9] cardiac troponin I (*TNNI3*)[10] and cardiac α-actin (*ACTC1*).[11] Most of these genes encode proteins of the myofilaments or Z-disc of the sarcomere as shown in Figure 2. More than 1,400 mutations have been described in association with HCM. Pathogenic variants affecting the *MYBPC3* and *MYH7* proteins are responsible for up to 50% of all clinically recognized cases of HCM. A disease–causing pathogenic variant is found in approximately 30-60% of HCM probands.

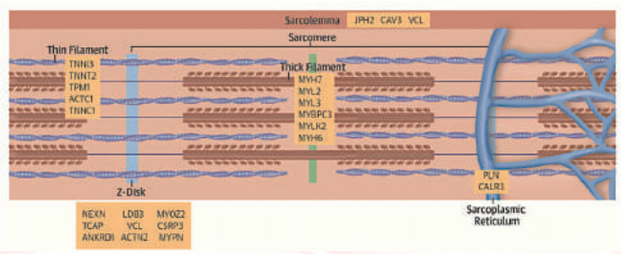


Figure 2. A Schematic of Definitive and Posited HCM genes with the Subcellular Localisation of the Encoded Proteins. Burke MA, et al. Clinical and Mechanistic Insights into the genetics of Cardiomyopathy. *J Am Coll Cardiol* 2018;68:2871-2886.

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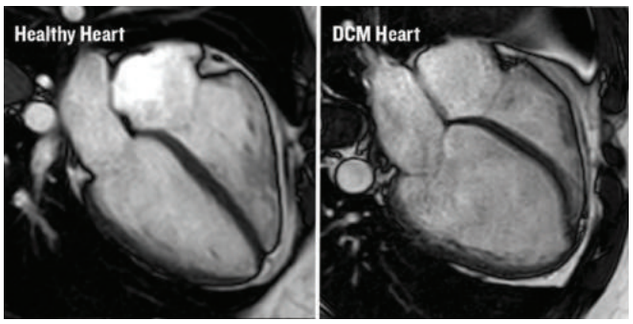

Figure 3. CMR Images of a Healthy Heart and a DCM Heart. https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2018/march/largest-ever-study-of-killer-heart-condition.

These genetic variants affect the biochemical and mechanical function in several ways. The myosin head region is the domain that generates force, hydrolyzes adenosine triphosphate and interacts with regulatory light chain, troponin T, and actin. Mutations in this domain exhibit biophysical properties that enhance contraction, but impair relaxation. Mutations in *MYBPC3* modulate contractile performance through interaction with myosin and titin. HCM mutations increase the energetic cost of contraction and also cause increase in calcium release causing diastolic dysfunction.[12]

The large numbers of HCM-causing genetic variants in different sarcomeric genes together with genetic, epigenetic and environmental modifiers explains why the genotype alone cannot predict patient specific clinical manifestations of HCM. There are several *MYH7* variants that cause significant cardiac remodeling with an increased risk of SCD and an increased risk for developing end-stage heart failure.[13] Some *TTN2* variants are associated with less hypertrophy but a higher risk in SCD.[7] Having more than one pathogenic variant results in a worse phenotype and prognosis.[13]

GENETICS IN DILATED CARDIOMYOPATHY

DCM is characterized by the enlargement of the left ventricular chamber accompanied with systolic dysfunction.[1] Histologically myocyte enlargement, cellular apoptosis and myocardial fibrosis are present, causing arrhythmias and heart failure. This cardiomyopathy is the commonest referral for heart transplantation. Around 50% of non-ischaemic DCM have no obvious aetiology, and in both familial and sporadic cases, genetic causes are increasingly identified.[14] Early population echocardiography studies estimated the prevalence of unexplained DCM as 1:2,500.[15] but recently epidemiological and heart failure data suggest a much higher prevalence of DCM as high as 1:250.[16] This matches the prevalence of likely pathogenic variants identified by next-generation sequencing.[17] Therefore there should be approximately 180-1,800 individuals affected with this condition in the Maltese population.

Figure 3 shows cardiac MRI images comparing a healthy heart to one affected with DCM.

Patients with DCM may be asymptomatic at first but they often present with acute shortness of breath, palpitations and lower limb oedema. Again, unheralded syncope may occur in this group of patients secondary to ventricular arrhythmias. The treatment in DCM is to prevent further negative remodeling of the myocardium and protect the individual from SCD. Fluid overload is treated with loop diuretics but aggressive medical treatment is commenced to improve the left ventricular function. This medication includes ACE-inhibitors, carvedilol and spironolactone. Novel medications such as angiotensin receptor-neprilysin inhibitors and dapagliflozin have been found to further improve the myocardial strength and together with the previously mentioned medications, also reduce hospitalization and mortality. If patients remain symptomatic at NYHA II or more with an EF of ≤35% despite optimal medical therapy, an implantable cardiac defibrillator or cardiac resynchronisation therapy (depending on the width of the QRS on ECG) should be considered.

In DCM, most genetic variants are transmitted as dominant traits but a few exhibit recessive, X-linked and matrilinear inheritance. DCM-causing genetic variants exhibit incomplete and age-dependent penetrance with the phenotype expression being delayed until the fifth and sixth decade. The substantial genetic heterogeneity of DCM has made comprehensive genetic testing technically difficult and costly. Next-generation sequencing has allowed us to fully interrogate all DCM genes and this should substantially increase mutation detection in both familial and sporadic cases. DCM-causing genes encode for a diverse group of proteins that are important in: 1) generating and transmitting force, 2) sarcomere integrity, 3) cytoskeletal and nuclear architecture, 4) electrolyte homeostasis, as well as 5) mitochondrial function and transcription.

Pathogenic variants in the titin (*TTN*) gene, which encodes for the titin protein in the sarcomere are the commonest cause of DCM accounting for 15 to 20% of cases.[18] Mutations that truncate the titin protein, such as non-sense, frameshift, or splice-site variants co-segregate in familial DCM and display nearly complete penetrance after 40 years of age. Phospholamban variants cause DCM by altering calcium homeostasis as it regulates calcium uptake by the sarcoplasmic/endoplasmic reticulum. The Arg9Cys mutation in *PLN* is particularly severe causing progressive heart failure requiring early heart transplantation.[19] Some mutations in *SCN5A* have also been implicated in DCM. This gene encodes for the sarcolemmal transmembrane cardiac voltage–gated sodium channel, that functions in developing cardiac action potentials. *SCN5A* mutations cause a high burden of arrhythmias and are responsible

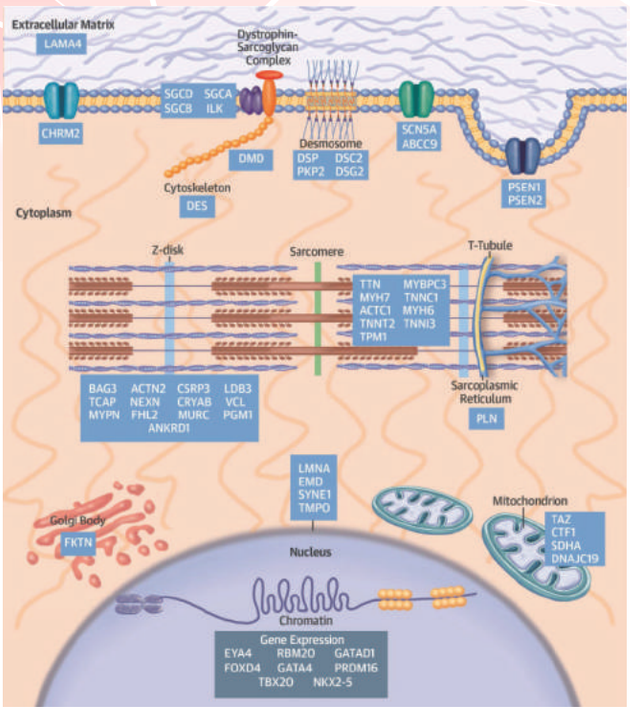

Figure 4. Schematic of Definitive and Posited DCM Genes with the Subcellular Localization of the Encoded Proteins. Pathogenic genes encode proteins that participate in many diverse biological processes of cardiomyocytes. Burke MA, et al. Clinical and Mechanistic Insights into the Genetics of Cardiomyopathy. *J Am Coll Cardiol* 2016;68(25): 2871-2886.

for causing Brugada syndrome, idiopathic ventricular fibrillation and familial atrial fibrillation.[20]

Multiple DCM genes cause both heart and skeletal muscle phenotypes, including *LMNA*, which encodes for the protein lamin A/C, a protein expressed in the inner nuclear membrane that plays a role in the maintenance of the proper nuclear structure. *LMNA* mutations occur in approximately 6% of DCM cases and also cause conduction disease. In fact, conduction disease and atrial fibrillation often precede DCM that inevitably leads to heart failure.[21] *LMNA* mutations are highly predictive of progressive conduction disease and risk of SCD. Early assessment for prophylactic implantable cardioverter–defibrillator (ICD) placement to treat malignant ventricular arrhythmias should be considered.[22] Figure 4 is a schematic diagram showing the various DCM-causing genes and the location of their encoded protein within the myocyte.

GENETIC TESTING IN CLINICAL PRACTICE

Knowledge of the genetic cause of a cardiomyopathy in patients can improve clinical management and provides diagnostic certainty. It may also help to guide the use of emerging therapies that target the biophysical consequences associated with the mutations.[23] Genetic diagnosis enables cost-effective screening of first-

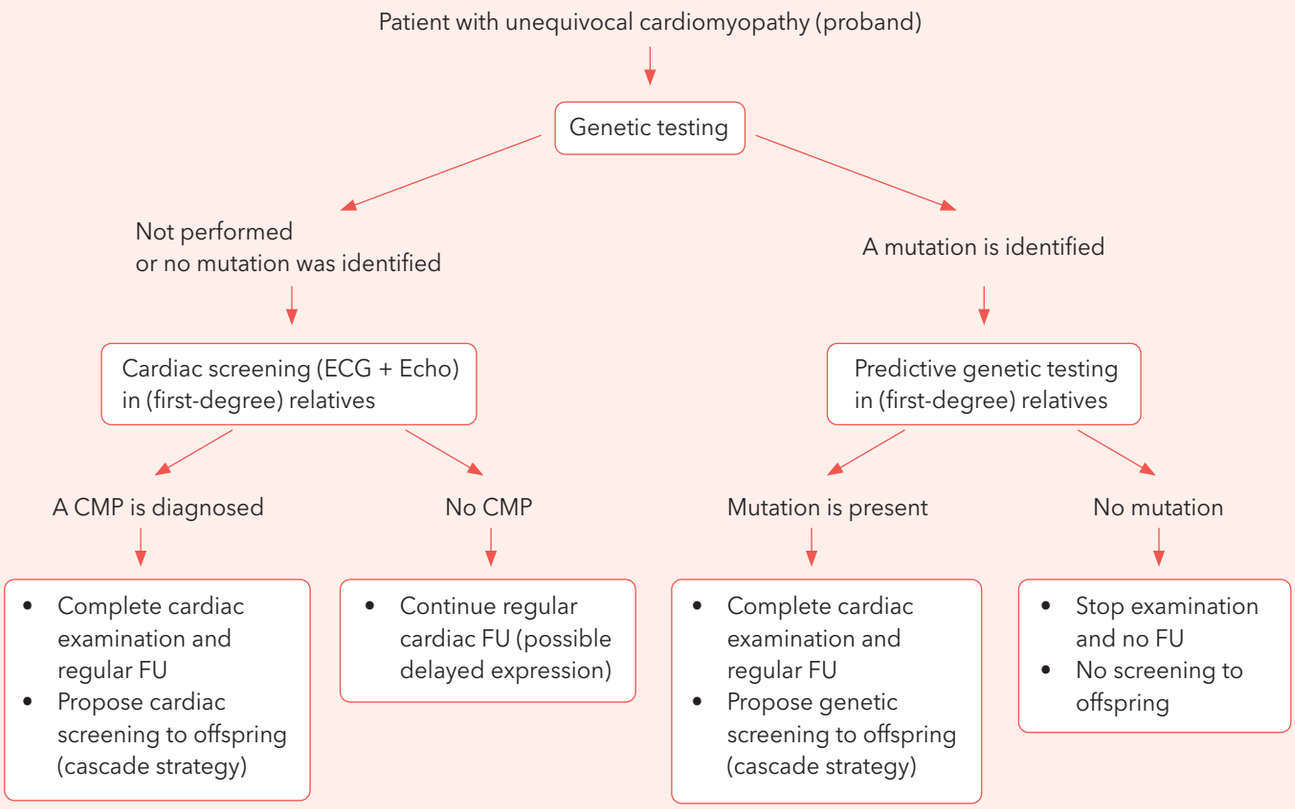

Figure 5. Organization of Family Screening. Charron P, et al. Genetic counseling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial diseases. *EHJ* 2010;31:2715-2728.

degree relatives, eliminating health care expenditures.[24] Cardiomyopathy gene panels continue to evolve thanks to next-generation sequencing and include comprehensive analysis of all genes implicated in HCM, DCM, ARVC and LVNC. If a disease-causing variant is not found, one may also use whole exome and whole genome sequencing since now the cost of genetics testing has become more affordable. Genetic testing may yield five distinct results: 1) identification of a definitely pathogenic variant. This outcome confirms the diagnosis, establishes the aetiology and identifies a target for familial screening, 2) identification of a probable pathogenic mutation, this potentially supports the clinical diagnosis but additional evidence such as familial co-segregation would be necessary to establish causality, 3) identification of a variant of unknown significance. This does not distinguish whether the variant is disease-causing or whether it represents a rare polymorphism unrelated to the disease and 4) identification of benign variants which are not disease-causing and occur in the general population.[25]

A cardiovascular genetic service has been setup at Mater Dei Hospital in 2020 in a joint effort between the cardiology and genetics departments. Thanks to this service cardiomyopathy patients who are seen at the inherited cardiomyopathy clinic may have genetic studies performed. When a definite pathogenic variant is found in the proband, targeted cascade genetic screening may be done on the first-degree relatives. In this way first-degree relatives who are genotype negative may be discharged from the clinical screening program. On the other hand regular clinical screening will continue on the genotype -positive individuals as seen in Figure 5.

Unfortunately there are times when cardiomyopathies present for the first time as SCD. In this situation genetics on the tissues may help us find the genetic variant responsible and hopefully protect the rest of the family. A family history of sudden death at a young age should alert one to the possibility of inherited cardiac disorders as a cause and referral for assessment of the relatives by a cardiologist is recommended.

CONCLUSION

Cardiomyopathies are a group of diverse disorders affecting the heart muscle with an increasing morbidity and mortality often affecting the young. Early diagnosis of these conditions allows for earlier and more aggressive management of this cohort of patients. Genetic studies have allowed us to improve the management of our cardiomyopathy patients as well as their relatives.

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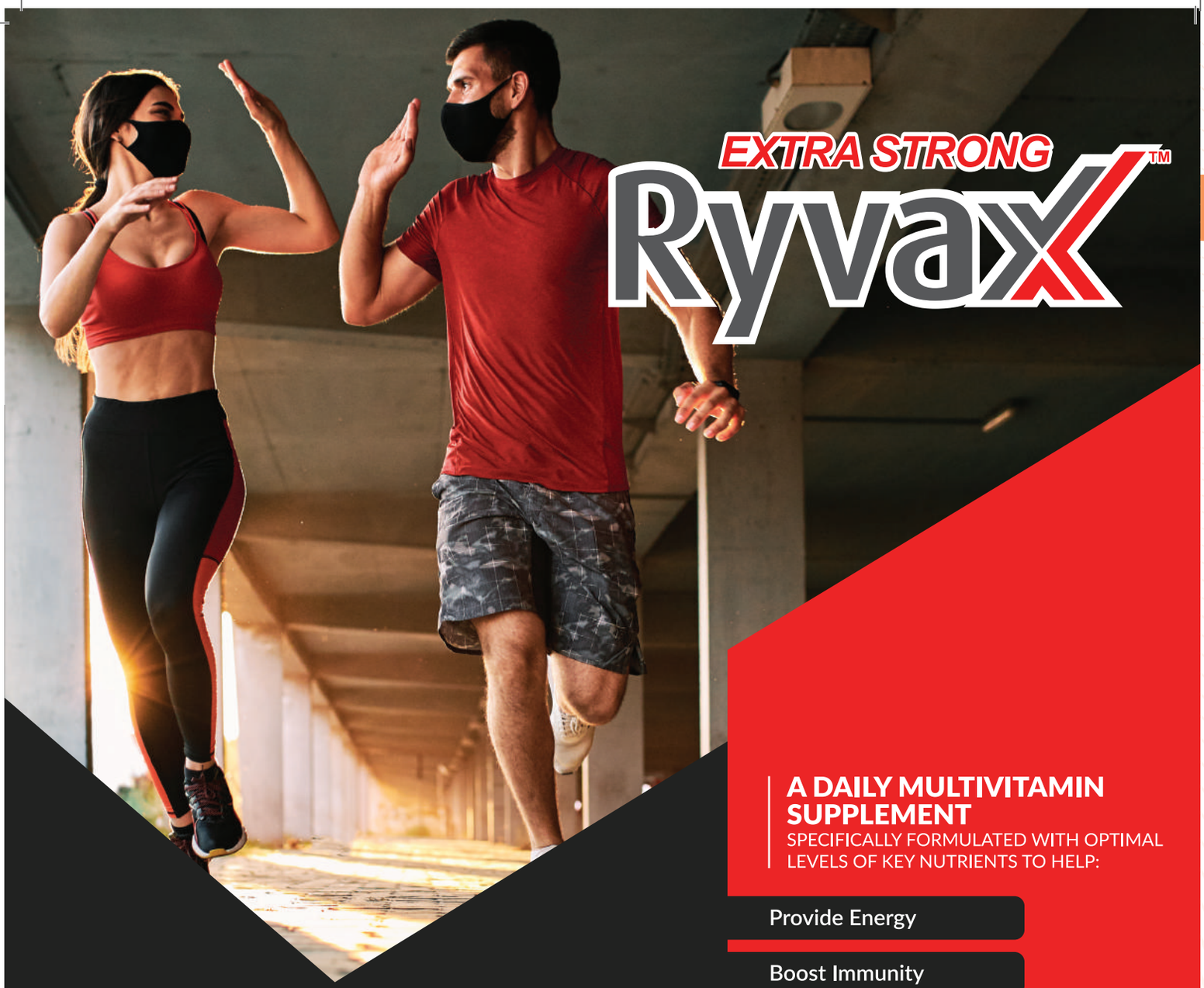

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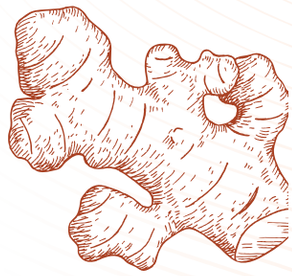
A Brief Review of the Effects of Ginseng and Ginger in Respiratory Tract Infections



1. INTRODUCTION

Infectious diseases are the leading cause of morbidity and mortality worldwide. They are primarily caused by either viral or bacterial infections.[1] Viruses are the most common cause of respiratory infections and facilitate secondary bacterial infections by aiding bacterial adherence, colonization, and translocation through the epithelial barrier of respiratory cells. This is called superimposed infection.[2]

By end of 2019, an outbreak of respiratory disease caused by SARS-CoV-2 virus occurred in China. COVID-19 was declared by the WHO a Public Health Emergency of International Concern in January 2020, and a pandemic in March 2020. Because of the importance of pulmonary infection associated with COVID-19, the present article will review the medicinal benefits of two species of plants, ginseng and ginger, in the management of upper and lower respiratory tract infections (URTI; LRTI), knowing that many food supplements and nutraceutical products contain ingredients originating from them.

2. GINSENG

The name 'ginseng' is widely understood to refer to the *Panax* species which belongs to the family Araliaceae. The *Panax* species is mostly found and cultivated in temperate zones particularly in North America and Asia. *P. ginseng* C.A. Meyer is the most widely used since it is considered as one of the most important tonic drugs.[3]

Different ginseng plants share in common their content of numerous pharmacologically active ingredients mainly ginsenosides, saponins, phytosterols, polyacetylenes, vitamins, nitrogenous substances, and minerals. Ginsenosides are the main active ingredients in ginseng known to possess enhanced therapeutic activity.[4] Ginseng has been shown to play a significant role in the protection from and treatment of many diseases and has been accepted as a natural product for health promotion,[4] enhancement of physical performance, and improvement of vitality and increase in resistance to stress and aging.[5-7] Ginsenosides have been shown to have different pharmacological effects, such as anti-diabetes,[8] anti-inflammatory,[9] anticancer,[10,11] and neuroprotective activity.[12,13] This paper will focus on the effects of ginseng on RTIs.

The literature relating to the use of ginseng extracts for the prevention and treatment of RTIs is exhaustive. Several in-vitro and preclinical and clinical studies have demonstrated the antiviral activity of ginseng on RTIs

arising from influenza virus, respiratory syncytial virus (RSV), rhinoviruses or of bacterial origins, example, *Streptococcus pneumoniae*.[14] Different observational studies have demonstrated the efficacy of ginseng on the course of respiratory diseases. The following are some examples.

Two randomized double-blind placebo-controlled studies in a cohort of patients aged 16-65 years,[15] and elderly subjects (81-84 years)[16] in an assisted living setting, including nursing homes investigated the relationship between ginseng and the incidence of influenza and cold symptoms. A significant decrease in severity of symptoms, occurrence of less cold or influenza episodes and shorter duration of the disease was observed in those who received ginseng versus placebo.

Predy et al.[15] found that the mean number of cold episodes per person was lower in the ginseng group than in the placebo group (0.68 v. 0.93, difference 0.25%, 95% confidence interval [CI] 0.04-0.45). The proportion of subjects with two or more verified colds during the 4-month period was significantly lower in the ginseng group than in the placebo group (10.0% v. 22.8%, 12.8% difference, 95% CI 4.3-21.3), as were the total symptom score (77.5 v. 112.3, difference 1.5%, 95% CI 1.2-2.0) and the total number of days cold symptoms were reported (10.8 v. 16.5 days, difference 1.6%, 95% CI 1.3-2.0).

In keeping with the above, McElhaney et al.[16] found that the incidence of influenza was greater in the placebo group (7 cases/101 subjects) than the ginseng-treated (1/97) groups (odds ratio (OR)=7.73, P=0.033). The combined data for influenza and RSV illness was also greater in the placebo groups (9/101) than ginseng-treated (1/97) groups (OR=10.50, P=0.009), for an overall 89% relative risk reduction of acute respiratory illness in the ginseng groups.

Another study aiming at determining the effect of ginseng administration on the potentiation of influenza vaccination showed that those who received the vaccine together with ginseng had a statistically lower incidence of influenza compared to the group who received a placebo with the influenza vaccine (13% vs 37%, p <0.001). Also, when measuring antibody titers at week 8 post-vaccination, these increased by 59% in the ginseng group vs. placebo group (171 units vs 272, p<0.0001). Natural killer (NK) activity levels at weeks 8 and 12 were nearly twice as high in the ginseng group as compared to the placebo group (p < 0.0001), indicating a higher early antiviral activity.[17]

There are currently two ongoing clinical trials registered in the EU Clinical Trials register [clinicaltrialsregister.eu] relating to ginseng. These are:

1. **EudraCT number:** 2017-003271-61 - Phase IIa (therapeutic exploratory), multicenter, randomized, double-blind, placebo-controlled, 2-stage, 4-arm study exploring the effect of BST204 [ginseng extract] on cancer-related cachexia in patients with gastrointestinal or non-small-cell lung cancer.
2. **EudraCT Number:** 2010-020504-30 - GATAC: Asian ginseng (Panax Ginseng) for the treatment of cancer-related fatigue: a randomized, double-blind controlled study.

Mechanism of Action

Some of the plausible mechanisms for ginseng-mediated viral inhibition are improvements in systemic and mucosa-specific antibody responses, serum hemagglutinin inhibition which is indicative of a good antibody response, lymphocyte proliferation, cell survival rate, and viral clearance in the lungs. Moreover, ginseng reduces the expression levels of proinflammatory cytokines, including IFNγ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL-8 implicated in the triggering of the cytokine storm that is responsible for the development of acute respiratory distress syndrome (ARDS) and subsequent mortalities such as the one seen in complicated COVID-19 infection.[14] In the case of bacterial infections, ginseng acts by lessening pro-inflammatory cytokine production and activating phagocytes and NK cells responsible for the killing of the infecting microorganism. In addition, ginseng inhibits biofilm formation and induces the dispersion and dissolution of mature biofilm making the eradication of infectious bacteria more vulnerable to antibiotic activity.[14]

3. GINGER

Ginger, scientifically known as *Zingiber officinale* is a commonly consumed dietary condiment in many culinary cultures. The plant has a long history of cultivation in the Asian subcontinent[18] and is generally considered to be safe even in pregnant women where it is given to treat morning sickness.[19]

Numerous active ingredients are present in the rhizome including terpenes and phenolic compounds.

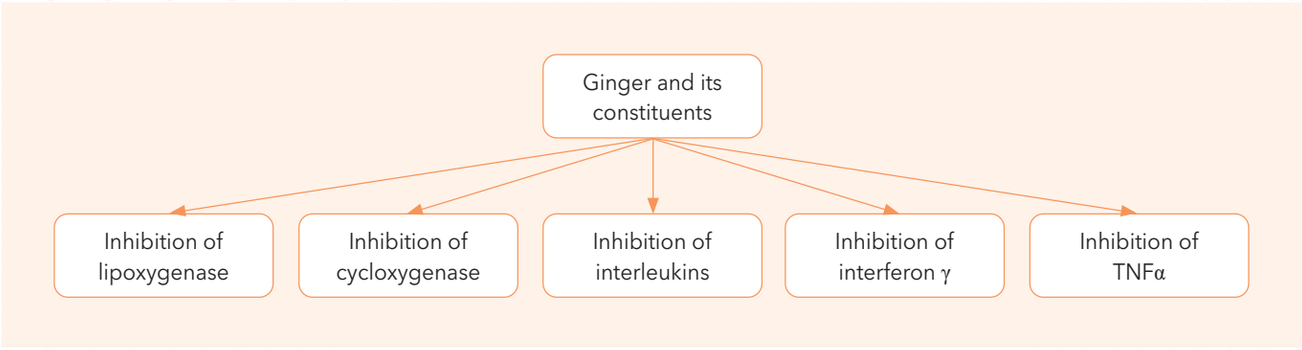


Figure 1: Summarization of the Immunomodulatory and Anti-inflammatory Effect of Ginger and Ginger constituents. Adapted from Rahmani AH (2014).[20]

Terpene components of ginger include zingiberene and α-curcumene. Phenolic components include gingerol, zingerone, gingerdione, paradol and shogaol. Taken together, these components are known to possess preventive and curative properties against various diseases. A review conducted by Rahmani et al (2014) concluded that the main biological effects of ginger, studied in-vitro as well as through preclinical and clinical studies, demonstrate anti-oxidant, anti-tumor, anti-inflammatory, anti-infectious, anti-obesity and antidiabetic activity. The review also discusses the beneficial hepato-, gastro- and neuroprotective effects of ginger.[20]

Similar to ginseng, this scientific review on ginger will focus on its effect on RTIs. As discussed, it is wellestablished that increased circulating levels of proinflammatory cytokines correlate to the severity of an infection.[21] In keeping with this, strenuous exercise, stress hormones and oxidative stress are examples of physiological stimuli that modulate cytokine production. The systemic inflammatory response which arises from prolonged aerobic exercise in athletes may lead to URTIs due to a suppression of the immune system.[21] The use of ginger extracts for a period of 12 weeks in healthy athletic volunteers who undergo intense exercise has been found to significantly reduce the production and release of IL-1β and IL-6 as well TNF-α compared to athletes who received placebo.[21] Interventions to dampen increases in cytokines implicated in inflammatory processes would seemingly justify their use to prevent or decrease infection.

A study conducted by Vahdat Shariatpanahi et al. (2013) concluded that the addition of ginger to the diet of ARDS patients for ten days led to a significant improvement of their respiratory illness, when compared to ARDS patients who were not given ginger. Patients taking ginger had a significant improvement in their oxygenation ($p<0.003$) and static compliance of their lungs (low lung stiffness -$p<0.01$) with a decrease in the duration of mechanical ventilation ($p=0.02$) and a shorter stay in intensive care units ($p=0.04$). This correlated with a significant decrease in pro-inflammatory cytokines IL-1, IL-6, and TNFα and an increase in glutathione ($p<0.05$).[22]

With regards to bacterial infections, the susceptibility of 17 bacteria species associated with RTIs was tested in-vitro against specific ginger extracts. Gram-positive bacteria resistant to cloxacillin, co-amoxiclav, tetracycline and erythromycin and gram-negative bacteria resistant to co-amoxiclav, tetracycline and amoxicillin were shown to be all susceptible to 200 - 400 mg/ml of ginger extract preparation but more to the methanolic than the aqueous extracts. While the mechanism of action needs to be further elucidated, ginger could show benefit in patients with lower RTI.[23]

There is currently one ongoing clinical trial registered in the EU Clinical Trials register [clinicaltrialsregister.eu] relating to ginger, i.e. Ginger, ginger-avocado-soy, glucosamine sulfate and ginger-ibuprofen in relation to chronic low back pain - a randomised double-blind, placebo-controlled clinical trial with parallel groups for 3 months to illustrate joint health [**EudraCT Number:** 2005-002691-1].

Mechanism of action

Many studies have demonstrated that ginger possesses antioxidative properties and plays a role in scavenging superoxide anions, hydroxyl radicals and other free radicals.[20] Figure 1 summarizes the immunomodulatory and anti-inflammatory effect of ginger. In animal studies, gingerol inhibited lipid peroxidation in liver microsomes.[20] Shogaol and gingerdione exert potent inhibition of nitric oxide (NO) synthesis in activated macrophages.[24] While NO plays a beneficial role in normal physiologic situations, increased NO production and release from macrophages is involved in the pathogenesis of inflammatory disorders of the joint, gut and lungs hence the benefits of curbing these effects.[25,26]

4. FROM PLANTS TO CONSUMPTION IN FOOD SUPPLEMENTS AND NUTRACEUTICALS

Many cultures recognize the benefits of ginseng and ginger plant extracts and use them in traditional medicine. The European Food Safety Authority (EFSA) has developed the "Qualified Presumption of Safety (QPS)" approach for

the assessment of botanicals or botanical preparations in food supplements or nutraceuticals.[27] The aim of this assessment is to help manufacturers produce and deliver products with tested ingredients, safe and free of contaminants. EFSA imposes stringent quality checks on compounds before being manufactured into supplements. These relate to the screening for contaminants such as radioactive material, heavy metals (i.e. cadmium, mercury, lead, arsenic, etc.), high potency carcinogens (i.e. aflatoxin-like), inorganic components, proteins and steroids, all substances known or predicted to bioaccumulate, nanomaterials, solvent residues or any other known chemical structure with unknown toxicity profile. Also, the analysis comprises looking for contamination with microorganisms, including yeasts and molds, Salmonella, *E. coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*. Manufacturers should also include analyses on the physical properties of the product such as the appearance, odor, solubility, and moisture levels. Reference specification values for specific methods of analyses exist for each contaminant. Levels of contaminants should always remain below the reference value otherwise the produced batch is discarded by the manufacturer in accordance to Good Manufacturing Practice.

Herbal supplements always pose issues relating to safety. In this case, both ginseng and ginger have shown a very good safety profile in population studies. Taking ginger as an example, this has been safely administered to pregnant women for the treatment of nausea[19] and a review on the adverse events seen with short- and long-term use of ginseng show a similar safety profile between those who received the plant and those who received placebo.[28] In Malta, specific legislation governs the marketing of food supplements on the Maltese market. The main legislative tools are Subsidiary Legislation 449.36 (Food Supplements Regulations) and Subsidiary Legislation 449.46 (Labelling, Presentation and Advertising of Foodstuffs Regulation). These include the maximum permitted levels and guidance levels for vitamins and minerals. Of note is that the labelling, presentation, and advertising must not attribute to food supplements the property of preventing, treating, or curing a human disease or refer to such properties.[29]

5. CONCLUSION

This review on ginseng and ginger focused on their effects in preventing and treating RTIs in view of the fact that since March 2020, the world is living the pandemic of SARS-CoV-2. However, these products have undeniable proven benefits on other diseases like cancer and related conditions such as cachexia, and metabolic diseases. Whereas multiple in-vitro, pre-clinical and clinical testing have proven the efficacy and safety of these two compounds in RTIs, further investigation is needed to assess their possible or potential role in the protection against respiratory infections associated with COVID-19.

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DR PIERRE VASSALLO

Imaging Ovarian Tumours
Part II

INTRODUCTION

In the first article of this series we outlined the large spectrum of ovarian tumours which are grossly divided into four groups: epithelial surface cell tumours, germ cell tumours, sex cord/stromal tumours and metastases.[1]

A general introduction of the subtypes of each tumour group was presented and the most common tumour group, the serous epithelial tumours, was discussed in more detail.

This second article in the series will discuss mucinous epithelial tumours, other less common epithelial tumour (endometrial and clear cell carcinomas) and epithelial-stromal tumours (Brenner tumours, adenofibroma and cystadenofibromas).

MUCINOUS EPITHELIAL TUMOURS OF THE OVARY

Mucinous epithelial tumours of the ovary are second most common type of ovarian tumour after serous epithelial tumours. They account for 10-15% of all ovarian tumours.[2]

Mucinous tumours are classified into three subgroups: mucinous cystadenomas, borderline mucinous tumours, and mucinous cystadenocarcinomas. Unlike serous epithelial tumours, in which the high-grade serous cystadenocarcinoma appears to be a distinct entity from the serous cystadenoma, borderline serous epithelial tumour and low-grade serous cystadenocarcinoma, mucinous tumours appear to arise from the same continuum of tumours that range from the benign to the overtly malignant subtype.

Most mucinous tumours encountered are of the benign or borderline type; they tend to affect a younger age group and have an excellent prognosis.[3] In contrast, mucinous cystadenocarcinomas tend to occur in an older age group (mean 54 years) and have the poorest prognosis of all ovarian tumours.[4]

Mucinous tumours are more likely to be unilateral, multilocular, confined to the ovary and large on presentation. They often present with abdominal discomfort and distension.

In keeping with the above, mucinous epithelial tumours present on imaging studies as large, unilateral, multilocular lesions with cyst contents that show variation in signal intensity, attenuation, and echogenicity (MR, CT, US) depending on the viscosity of the mucinous content of the cysts.

Papillary projections are rare while calcifications are common in mucinous tumours; both features are in contrast to serous epithelial tumours.

Distinguishing between benign and borderline mucinous tumours may be very difficult. However the presence of numerous cystic spaces, high T1 and low T2 signal of cyst content, mural nodules and cyst walls, which are thicker than 5mm are suggestive of a borderline lesion[5] (Figure 1).

Benign and borderline mucinous tumours may contain solid components, which are often composed of fibrous tissue. An abundance of fibrous stroma has led to the term mucinous cystadenofibroma.[6]

Mucinous cystadenocarcinomas are usually larger (>10cm) and they contain numerus small cystic spaces and large solid components[7] (Figure 2).

Mucinous adenocarcinomas and, to a lesser extent, borderline mucinous tumours may exhibit seromucinous glandular cells that are similar to those seen in the gastrointestinal tract and in the cervical canal. In such situations, it is important to distinguish between a primary mucinous tumour of the ovary and a metastatic lesion to the ovary from a gastrointestinal primary neoplasm. Since primary mucinous neoplasms are usually large (>10cm) and solitary, a radiologic suggestion of small and bilateral mucinous tumours should prompt search for a gastrointestinal primary lesion.[8]

ENDOMETROID AND CLEAR CELL CARCINOMAS

Endometroid and clear cell ovarian tumours are almost always invasive and malignant. This is in contrast to serous and mucinous ovarian neoplasms. They are

usually detected early and present in the 5th decade. High grade endometroid carcinomas are often histologically indistinguishable from high-grade serous cystadenocarcinomas (HGSCs), which raises the question as to whether the former is really a distinct entity.

Clear cell carcinomas are associated with thromboembolic disease and paraneoplastic hypercalcaemia.

Both endometroid and clear cell carcinomas are frequently associated with endometriosis and also with Lynch syndrome, which often presents with a synchronous endometrial carcinoma.[9]

Endometroid and clear cell carcinomas have similar imaging features to other ovarian epithelial tumours with cystic and solid components; however they tend to have more solid components than serous and mucinous ovarian tumours (Figure 3). They may arise in an endometriotic cyst, where a mural enhancing nodule in the cyst wall may be the only indication of their presence, which should raise suspicion particularly in a woman aged 45 years or older.

BRENNER TUMOURS

Brenner tumours are rare epithelial-stromal tumours that are mostly benign and may co-exist with other epithelial neoplasms. They frequently contain amorphous calcifications and show low blood flow on colour Doppler ultrasound. Due to a large fibrous component, they show low signal on T2-w images (Figure 4). When lying adjacent to a cystic structure, the latter usually represents a co-existing epithelial lesion (usually mucinous cystadenoma). Cysts and areas of high T2 signal within Brenner tumours are rare and indicative of a malignant variety.

ADENOFIBROMA AND CYSTADENOFIBROMA

These are rare epithelial/stromal tumours that are almost always benign and often detected incidentally. Most are of the serous subtype but may be associated with other epithelial types. Their fibrous stroma may have hormonal activity.

They may show both solid and cystic components, absent colour Doppler flow, low T2 signal due to dense fibrous stromal components and minimal contrast enhancement (Figure 5). High T2 signal and stronger contrast enhancement are signs of a rare malignant variety called cystadenocarcinofibroma.

CONCLUSION

The above article concludes the subject of epithelial and epithelial/stromal ovarian tumours. The next and final article on the subject of ovarian tumours will discuss germ cell tumours and sex chord stromal tumours and metastases to the ovary.

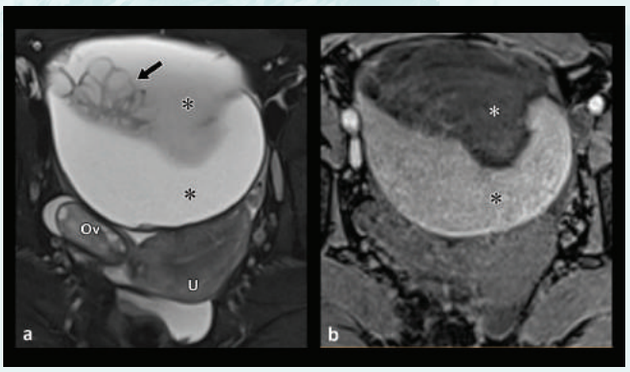

Figure 1. Borderline Mucinous Tumour: (a) T2-w transverse MRI scan showing a left ovarian tumour containing mucous of different signal intensities (*). Note the cluster of cysts (arrow) contained with the lesion. The normal right ovary (Ov) and uterus (U) are also shown. (b) T1-w transverse non-enhanced MRI scan shows low T1 signal in the mucous that showed high T2 signal in (a).

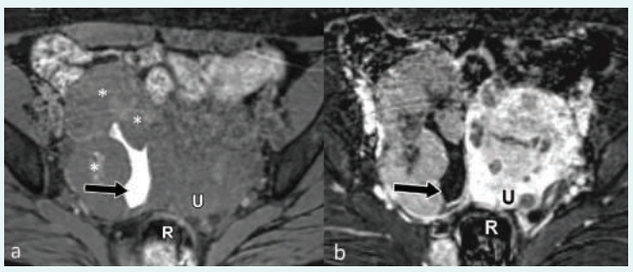

Figure 3. Endometroid Carcinoma: Pre-contrast (a) and contrast-enhanced (b) T1-w scans through the pelvis showing a right ovarian mass composed of mostly solid enhancing components (*) and a small cystic space with high T1 signal indicated haemorrhagic fluid. A fibroid uterus (U) and the rectum are also seen.

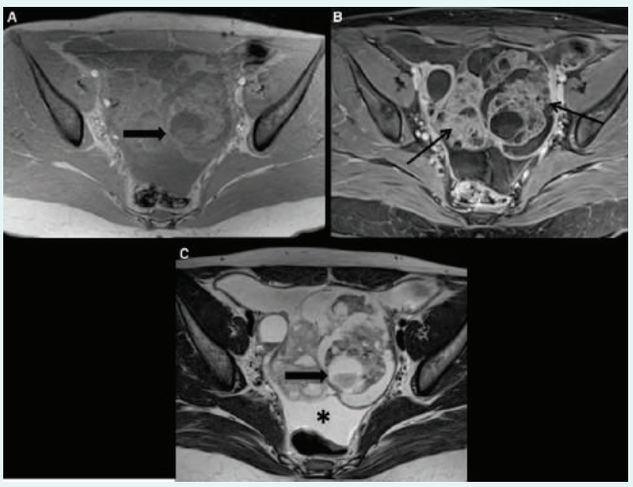

Figure 2. Mucinous Cystadenocarcinoma: T1-w fat saturated non-enhanced (a) and contrast enhanced (b) images and T2-w image through the pelvis showing a large complex mass containing numerous cystic spaces and marked enhancement of the intervening solid components (thin arrows). A fluid-fluid level (large arrow) indicates different compositions of mucous with low T2 signal (c) and intermediate T1 signal (a).

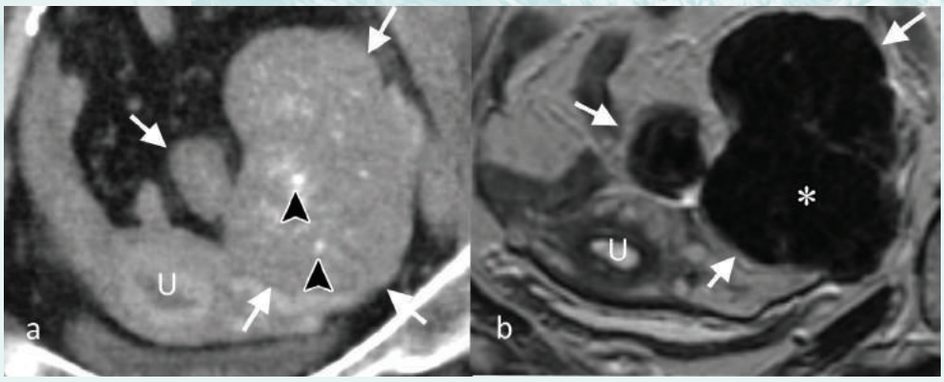

Figure 4. Brenner Tumour: (a) CT scan through a left ovarian mass (white arrows) that contains calcifications (arrowheads). (b) T2-w MRI scan showing large low signal areas in the mass (*) indicative of fibrous tissue. (U – uterus).

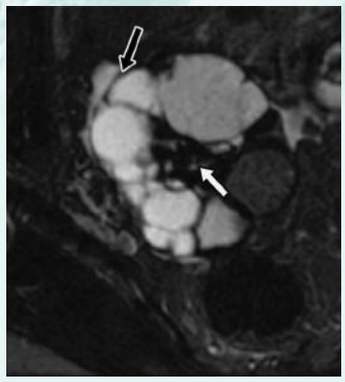

Figure 5. Cystadenofibroma: T2-w MRI scan showing a complex cystic mass with hypointense fibrous components (black arrow) and thick low signal septal walls (white arrows).

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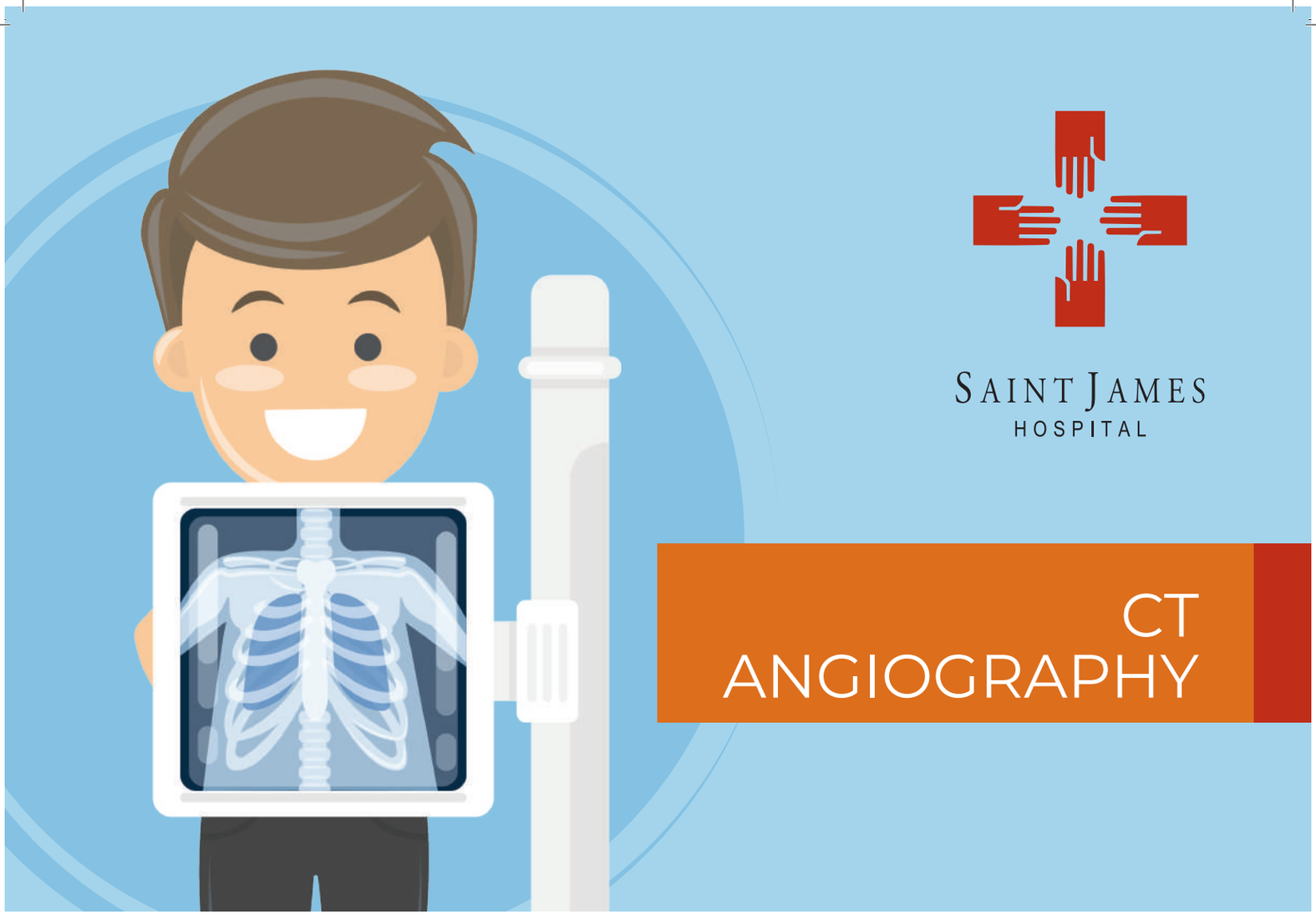
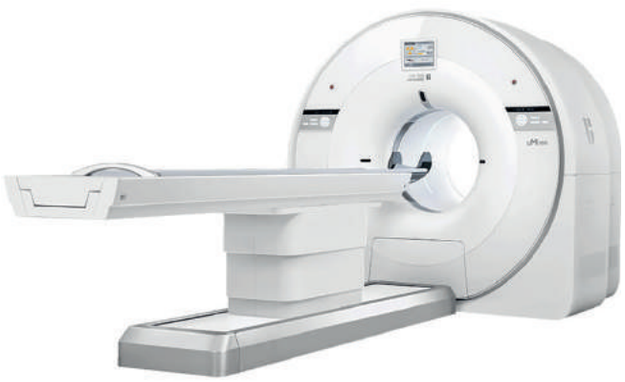


SAINT JAMES
HOSPITAL

CT ANGIOGRAPHY

What is CCTA?

Coronary computed tomography angiography (CCTA) is a heart imaging test that helps determine if plaque buildup has narrowed the coronary arteries, the blood vessels that supply the heart. Plaque is made of various substances such as fat, cholesterol and calcium that deposit along the inner lining of the arteries. Plaque, which builds up over time, can reduce or in some cases completely block blood flow. Patients undergoing a CCTA scan receive an iodine-containing contrast material as an intravenous (IV) injection to ensure the best possible images of the heart blood vessels.



What are some common uses of the procedure?

Many physicians advocate the use of CCTA for patients who have:

- suspected abnormal anatomy of the coronary arteries;
- low or intermediate risk for coronary artery disease, including patients who have chest pain and normal, non-diagnostic or unclear lab and ECG results;
- non-acute chest pain;
- new or worsening symptoms with a previous normal stress test result;
- unclear or inconclusive stress test result;
- new onset heart failure with reduced heart function and low or medium risk for coronary artery disease;
- intermediate risk of coronary artery disease before non-coronary cardiac surgery;
- coronary artery bypass grafts.

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