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Of dracunculiasis and 3-person IVF

When I was envisaging this editorial I was inclined to write about the medical advances being achieved in the field of parasitology. Indeed the WHO has recently stated that there are now only 542 known cases of Guinea worm, also called dracunculiasis, left worldwide, as of 2012, which represent a 48% decrease from 2011. In 1986 there were 3.5 million cases worldwide. The global eradication target date is 2015, which would hopefully place the Guinea worm as the second disease achieving global eradication since 1980, after smallpox.

I was also going to discuss another success story, also centred in Africa. mPedigree is a non-profit company based in Ghana which sells technology allowing people to use their mobile phone to verify if the medicines which they are going to use are counterfeit or not.

However as I was going to elaborate on these two achievements, I came across the 3-person IVF procedure. Basically it involves creating babies with genes obtained from 3 persons. The reason behind this novel technology, which is spearheaded by the UK, is precisely to offset rare mitochondrial disorders, by using mitochondrial DNA extracted from an egg of a 3rd donor. In this case, the UK’s Human Fertilisation and Embryology Authority has recommended that the child should have no right to know the identity of the person donating the mitochondrial DNA. Obviously from an ethical point of view this could be a slippery slope. Although the Human Fertilisation and Embryology Authority has clarified that only modifications to mitochondrial DNA will be allowed, what will refrain from an eventual manipulation of main nuclear DNA?

During the last years we have seen numerous provisions which remind me of Aldous Huxley’s Brave New World which I studied during my secondary education. During my lifespan, abortion, sperm and egg donation, surrogacy and a myriad of other technologies, the latest one being illustrated above, have been strengthened in order to facilitate our pains and meet our expectations. The British Surrogacy Arrangements Act was in fact published in 1985, almost 20 years ago, at a time when other populations were amusing themselves with other things such as the release of the first version of the Windows program by Microsoft.

In my opinion one should make available the latest technologies to improve the quality of life of people, however everything comes at a cost. I am sure that not everyone who is currently experiencing this changing paradigm will be paying a price, but society as a whole is inevitably subjected to that price. Our children will need to adapt to an increasingly hedonistic society, which may be more inclined to tweak nature’s course to adapt to its more comfortable and harmonised way of living.

Incidentally last month saw a US federal judge lifting the morning after pill age limit in the US. According to the judge, girls as young as 11 years have a right to gain access to the morning-after pill without a prescription. At times I wonder if I am experiencing a time warp...

Ian C Ellul

Sherlock Holmes and Dr Watson were going camping. They pitched their tent under the stars and went to sleep. Sometime in the middle of the night Holmes woke Watson up and said: “Watson, look up at the sky, and tell me what you see.”

Watson replied: “I see millions and millions of stars.”

Holmes said: “And what do you deduce from that?”

Watson replied: “Well, if there are millions of stars, and if even a few of those have planets, it’s quite likely there are some planets like Earth out there. And if there are a few planets like Earth out there, there might also be life.”

And Holmes said: “Watson, you idiot, it means that somebody stole our tent.”

Geoff Anandappa (Blackpool)
Patients do not need to hold their breath after inhalation

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Symbicort® contains budesonide (200mcg) and formoterol (6mcg) in a single inhalation.

Some inhalations with Symbicort may be needed in severe exacerbations of asthma.

If this occurs with asthma, it is recommended to seek medical advice immediately.

Inhalations should not be taken more than twice a day.

Inhalations may sometimes cause a mild increase in blood glucose levels, which may be sufficient to require supplementary medication. Therefore, patients should be aware of any changes in their blood glucose levels and if necessary, consult a medical professional.

Patients should be aware of any symptoms that may occur due to the inhalation of Symbicort, such as headache, tremor, or hoarseness. These symptoms may indicate that the dose is too high and should be reviewed by a medical professional.

Inhalations should be taken at least 8 hours apart, unless otherwise directed by a medical professional.

Patients should not stop taking Symbicort without consulting a medical professional, as this may cause rebound symptoms and worsen symptoms of asthma.

Inhalations may sometimes cause worsening of symptoms, such as exacerbations of asthma, during the first few weeks of treatment. Therefore, patients should be aware of any symptoms that may occur due to the inhalation of Symbicort.

Inhalations may reduce symptoms of asthma by virtue of the adrenergic beta agonist, as well as the glucocorticosteroid budesonide. Therefore, patients should be aware of any symptoms that may occur due to the inhalation of Symbicort.

Inhalations may be difficult for patients with COPD, as they have difficulty with inspiratory flow. Therefore, patients should be aware of any symptoms that may occur due to the inhalation of Symbicort.

Inhalations may sometimes cause worsening of symptoms, such as exacerbations of asthma, during the first few weeks of treatment. Therefore, patients should be aware of any symptoms that may occur due to the inhalation of Symbicort.
Superior lung function improvement (FEV1 vs salmeterol and formoterol)

Rapid onset of action within five minutes from the first dose

Significant reduction in the use of and need for rescue medication

A good overall safety and tolerability profile

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- Rapid onset of action within five minutes from the first dose
- Significant reduction in the use of and need for rescue medication
- A good overall safety and tolerability profile
- Available in 150µg and 300µg: two dose strengths allowing flexibility when treating patients with COPD
- Onbrez® Breezhaler® allows patients to hear, feel and see that they have taken the full dose correctly
It is evident that tobacco use can lead to nicotine dependence and serious health problems. It is equally evident that cessation can significantly reduce the risk of suffering from smoking-related diseases. Total cessation is the only intervention with the potential to reduce tobacco-related mortality in the short- and medium-term, whilst a reduction in consumption has a limited effect.

Some smokers quit without using evidence-based cessation treatments. However, the following treatments have been proven to be effective for smokers who want help to quit:

- Brief clinical interventions (doctors’ advice and assistance on quitting)
- Counselling (individual, group, or telephone counselling)
- Behavioural cessation therapies (training in problem solving)
- Cessation medications

Simple advice from a physician has been shown to increase abstinence rates significantly compared to no advice. As a physician you are in a unique position because of your established relationship with the patient. It is important that up-to-date records of the smoking status of all patients are kept, all smokers are advised on a regular basis to stop and where possible offer them assistance with doing so. It is also important that this advice is repeated as needed.

Mark P et al[^2] have emphasized the need for physicians to be trained in the use of brief counselling techniques. The effectiveness of training has been further supported by Caplan et al[^3] who have shown that training can help break barriers to the provision of smoking cessation. Training of other health professionals has also shown to be beneficial. A model developed by Hazel K Sinclair et al[^4] has shown that training of community pharmacists also results in higher smoking cessation rates, indicating that community pharmacy personnel have the potential to make a significant contribution to national smoking cessation targets.

A tool kit to help strengthen the skills needed to trigger and facilitate the quitting process has been developed by the Health Promotion and Disease Prevention Directorate as part of the actions recommended from the National Cancer Plan.

This follows the **ABC process:**
- **Ask** about smoking status
- **Brief Advice:** advice on how to stop, about available programs and/or prescribe nicotine replacement therapy
- **Cessation Support:** referral to quit-line or smoking cessation programs

Smoking cessation programs are organised by the Health Promotion and Disease Prevention Directorate. These are free of charge and are carried out during the evenings in various health centres including Paola, Mosta, B’Kara, Floriana, Gzira, Qormi and Gozo. Hence patients can be referred to these classes. For further information and copies of the tool kit and smoking cessation application forms kindly call the directorate on 23266000 or email health.pro@gov.mt

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**References**


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All material is also available online at [https://ehealth.gov.mt/HealthPortal/health_promotion/library/publications.aspx](https://ehealth.gov.mt/HealthPortal/health_promotion/library/publications.aspx)
Positron Emission Tomography (PET)

Why PET/CT?
Like other Nuclear Medicine investigations, Positron Emission Tomography (PET) differs from other imaging modalities in that it demonstrates function of the system being investigated rather than anatomy. Tracer distribution and concentration is followed, thus the various molecular events taking place are monitored.

In the case of PET/CT a Nuclear Medicine Physician has the further advantage of being able to interpret the superimposed images of a PET and CT scan concomitantly. Adding metabolic to morphologic data in one session, without moving the patient and with minimal delay between reconstruction and fusion of the two image data sets, is advantageous synergistic in giving the referring physician a more complete picture of the disease status.

PET/CT involves a simple intravenous injection of mildly radioactive tracers labeled with a positron emitting isotope. There are practically never any side effects and the procedure is of minimal inconvenience to the patient. Even renal failure patients can perform a PET/CT.

Clinically, PET/CT has become an integral part of patient management in oncology, neurology, cardiology and inflammatory pathologies.

By far, oncology accounts for most PET/CT applications. The most widely available PET/CT radiopharmaceutical today is an analogue of glucose labeled with $^{18}$F, fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) which has a half-life of 110 minutes. Its application in oncology is related to the fact that cancerous cells have higher metabolic rates. They use more glucose than normal cells since malignant transformation is associated with increasing energy demands. $^{18}$F-FDG PET/CT has become an established technique for diagnosis, staging, restaging, and detection of residual/recurrent cancer, follow-up of a multitude of cancers, the metabolic characterisation of lesions and also in planning therapies.
Implicated Pathological Functions of TE (e.g. HERVs; LINEs, and SINEs)

(i) Cancer

It is being postulated that in somatic cells, the transposition of HERVs and other TEs may land into tumour suppressor genes and this could cause neoplastic transformation. It is a known fact that many cancers feature global DNA hypomethylation and localized hypermethylation of CpG islands of tumour suppressor genes.¹ Since DNA methylation is one of the epigenetic mechanisms that cells have evolved to check on TEs from being unleashed and doing havoc in their genome, it is being postulated that with the event of global DNA hypomethylation, the TEs transpose because the epigenetic constraints are lifted. If some TEs end up in or near the promoter region of tumour suppressor genes, the chromatin structure is heterochromatized (i.e. become condensed and compacted) and hence silenced for transcription. With the function of tumour suppressor genes switched off, neoplastic transformation sets in. Generally, tumorigenesis occurs because the silenced tumour suppressor genes result in (i) altering the cell cycle, (ii) blocking apoptosis or (iii) blocking DNA repair.⁶ Later on as the global DNA hypomethylation continues, genes inhibiting cell invasion and dissemination also get involved and are silenced by their promoter undergoing CpG island hypermethylation.² Examples of such genes (called metastasis suppressor genes) that get silenced and result in dissemination, often normally code for proteins that make cells ‘stick’ together but not only (Table 11). Thus when they get silenced, the tumour cells do not ‘stick’ in the original site but start to detach, invade and disseminate.

Other retroelements that have been found to cause cancer are LINE-1 sequences, involving the myc gene in breast carcinoma and involving the APC (adenomatous polyposis carcinoma) gene in colon cancer. The HERV-K provirus family is implicated in several cancers. This is because members of this family have open reading frames (ORFs) for all their viral genes. An ORF is a DNA sequence without a stop codon in the given frame. This translates that HERV-K are the most likely to be biologically active and potentially pathogenic because their sequences are most likely to be expressed.

### Table 12: Putative association of HERVs in cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Implicated HERV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>HERV-K</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>HERVs</td>
</tr>
<tr>
<td>Melanoma</td>
<td>HERV-K</td>
</tr>
<tr>
<td>Myeloproliferative disease</td>
<td>HERV-K</td>
</tr>
<tr>
<td>Testicular tumours (seminomas; teratomas)</td>
<td>HERV-K (sub-group HML-2)</td>
</tr>
</tbody>
</table>

### Table 11: Some examples of ‘Metastasis Suppressor Genes’ and the effects of their products

<table>
<thead>
<tr>
<th>Genes ® Proteins</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>laminin genes → laminins</td>
<td>Laminins induce and maintain cell polarity; establish barriers between tissue compartments; organize cells into tissues; protect adherent cells from detachment-induced cell death.</td>
</tr>
<tr>
<td>TIMP genes → Tissue inhibitors of proteinases (TIMPs)</td>
<td>TIMPs antagonize matrix metallo-proteinases (thus suppress tumour growth, angiogenesis, invasion and metastasis).</td>
</tr>
<tr>
<td>semaphorin genes → semaphorins</td>
<td>Semaphorins are axon guidance proteins that block VEGF (vascular endothelial growth factor) autocrine activity.</td>
</tr>
<tr>
<td>Thrombospondins (THBS) genes → thrombospondins</td>
<td>Thrombospondins are proteins that regulate tissue genesis and remodelling.</td>
</tr>
<tr>
<td>Cadherin genes (e.g. E-Cadherin, H-cadherin, R-cadherin) → cadherins</td>
<td>Cadherins are a group of cell adhesion molecules that form stable cell-cell junctions.</td>
</tr>
</tbody>
</table>
Table 13: Putative association of HERVs in autoimmune diseases

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>HERV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>HERV-K</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>HERV-K</td>
</tr>
<tr>
<td>Insulin Dependent diabetes mellitus</td>
<td>HERV-K</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>HERV-E</td>
</tr>
</tbody>
</table>

Table 14: Putative association of HERVs in neurological diseases

<table>
<thead>
<tr>
<th>Neurological Disease</th>
<th>HERV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>HERV-W, HERV-K</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>HERV-W</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>HERV-W, HERV-H</td>
</tr>
</tbody>
</table>

(ii) Autoimmune Diseases
- Rheumatoid Arthritis (RA)
  The expression of HERV-K18 was up-regulated in patients with juvenile rheumatoid arthritis. The possible mechanism offered is that of a super-antigen (SAg) stimulation in auto-reactive T cells causing the autoimmunity.
- Systemic Lupus Erythematosus (SLE)
  Here it is being implicated that HERV-K env protein is the culprit causing autoimmunity through molecular mimicry and immunomodulation. Molecular mimicry refers to similar structures that molecules share between them despite arising from dissimilar origins. For example the molecules might share some linear amino acid sequences or their 3-D conformational fit, even though their origins are separate (e.g. a virus and a normal host self determinant). In SLE, it is being implied that the determinant shared by the host and the HERV-K env protein evokes an immune response and causes the destruction of cells and tissue.
- Insulin Dependent Diabetes Mellitus (IDDM)
  The culprit here is a viral sequence appertaining to a HERV-K family. Specifically, HERV-K env encodes a super-antigen which allegedly is being held responsible to play a part in the etiology of insulin-dependent diabetes mellitus (IDDM).
- Psoriasis
  Moles J. P. et al. found 3 HERV families in psoriatic lesions, (HERV-W, HERV-K, and HERV-E). They proposed that the expressed sequences of these HERVs have roles in the development of psoriasis and are doing further research in this regard.

(iii) Neurological Diseases
- Schizophrenia
  When sera of schizophrenic patients are tested with antibodies to HERVs, a greater frequency of positives is found than control subjects. Researchers continue to look at a possible link between HERVs and schizophrenia. Karlsson et al. have provided intriguing data that implicate the possibility of this link. The culprit that they implicate belongs to HERV-W. Indeed, they found that RNA transcripts homologous to members of this family are up-regulated to different levels in the frontal cortex obtained post-mortem from schizophrenic patients.
- Motor Neuron Disease
  Here elevated expression of HERV-W env and gag genes have been detected and proposed in the pathogenesis.
- Multiple Sclerosis
  HERV-W RNA has been detected in the circulating viral particles (called Multiple Sclerosis associated Retroviral element, MSRV), which for many years have been associated with the evolution and prognosis of Multiple Sclerosis. Specifically, HERV-W env gene codes for an envelope protein called syncytin-1. Here syncytin, unlike its beneficial function in the morphogenesis of the placenta, acts as a powerful immuno-pathogeneic molecule that triggers a pro-inflammatory and autoimmune cascade.

(iv) Other Medical Diseases Where TEs Are Proposed To Be Involved
Table 15 gives other examples of medical diseases were retroelements cause insertional mutagenesis and re-combinations in specific genes.

Repercussions
A very promising transposable element that is being used by researchers worldwide is the Sleeping Beauty (SB) TE. This is an ancient transposon from fish which has been reconstructed. Its usefulness is three-fold. Firstly, it is being used to gain knowledge into the basic molecular machinery of DNA transposition and its regulation in vertebrate cells. Secondly it is being used as a vector for insertional mutagenesis screens in model organisms; this is because SB can transpose in cells of different vertebrate classes in tissue culture. Such screens help in the discovery of genes. Thirdly, it is intended to be applied in human therapeutics.

In the field of medical therapeutics, understanding the underlying processes of how these relic HERVs and other transposons bring about human diseases could help in their prevention and treatment. Just to give an example, in multiple sclerosis a new therapeutic approach is to target the human endogenous retroviral protein MSRV-Env, which as said above has been found to be a key factor in the pathogenesis of MS. A fully humanized monoclonal antibody is being proposed to target this pathogenic protein. But this is not all. Indeed, MSRV could be used as a biomarker for the prognosis of the disease since patients with higher loads of MSRV fair worse. Similar approaches could also be used for the other medical diseases mentioned in this essay.
Important strides are being made in the cancer field. For example HERVs transcriptomes (i.e. HERVs signatures) associated with specific types of cancer are being deciphered and databased. These are intended to be used in the future as a means for assessing (i) an individual’s risk status for cancer, (ii) the early detection of cancer and (iii) the monitoring of its treatment and prognosis. These signatures taken together with epigenetic signatures (e.g. DNA methylomes and histone codes) are very promising candidates as bio-indicators for the early detection of carcinogenesis. Again similar goals could also become applicable to other medical diseases where HERVs and epimutation signatures are found.

If as is being found HERVs and epimutation signatures cross talk in the pathogenesis of medical diseases, then as has been the case in some cancer types, epigenetic-based treatment strategies would become rational also. Already the FDA has approved the first generation of epigenetic-based drugs. Indeed, the use of such drugs is establishing that epigenetic modulation can be a feasible treatment option, not only for cancer, but also for the growing list of diseases where epigenetic mechanisms of gene expression underline their pathogenesis. And since epigenetic changes are thought to be responsible for a wide range of diseases, the scope of epigenetic therapy is likely to expand.

The four epigenetic drugs available for clinical use in the U.S. include two DNA demethylating agents, 5-azacytidine and decitabine, and two histone deacetylase (HDAC) inhibitors, vorinostat and valproic acid. At present the targets for epigenetic drugs are DNMTs and HDACs, the latter generating the most excitement. It is worth mentioning that since many other molecules are also involved in epigenetic mechanisms, there are other potential targets as well. Similar ‘bullet-targeting’ of other molecular players involved in HERVs-associated pathological pathways will surely be found and used in medical therapeutics.

**Conclusion**

For some HERV loci it has already been shown that they are implicated in certain gene expression and diseases. Large scale studies of HERV transcriptomes should be carried out to detail in the expression of more active HERV loci. This should be done in every human tissue both in health and in disease. Doing so one could then start to comprehend more the functions of HERVs in human diseases.

It is becoming clearly evident that an old relation in our genome is gaining new perspectives. But if the accumulating evidence definitely shows that this old relation is implicated in many of our medical diseases, then one could also surmise that these medical diseases that afflict us could be the prize that we have to pay for our marvellous evolution.

**Table 15:** Cases of insertional mutagenesis and re-combinations caused by retroelements

<table>
<thead>
<tr>
<th>Retroelement Involved</th>
<th>Gene Affected</th>
<th>Functional Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>LINE-1</td>
<td>Factor VIII</td>
<td>Haemophilia A</td>
</tr>
<tr>
<td>LINE-1</td>
<td>Dystrophin</td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td>SINE</td>
<td>Fukutrin</td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td>Alu</td>
<td>NF1</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>HERVs</td>
<td>AZFa (azoospermia factor a) region</td>
<td>Male infertility</td>
</tr>
</tbody>
</table>

**Table 16:** The four epigenetic drugs approved for clinical use in the US

<table>
<thead>
<tr>
<th>DNMTs inhibitors • 5-azacytidine • decitabine</th>
<th>DNA methyltransferase inhibitors</th>
<th>act as DNA demethylating agents and so reduce the levels of DNA methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDAC inhibitors • vorinostat • valproic acid</td>
<td>Histone deacetylase (HDAC) inhibitors</td>
<td>acetyl groups are not removed from histone tails</td>
</tr>
</tbody>
</table>

References

Takotsubo cardiomyopathy in a healthy twenty year old

Introduction

Takotsubo cardiomyopathy, also known as Transient apical ballooning syndrome, stress-induced cardiomyopathy and broken-heart syndrome, is a rare non-ischemic cardiomyopathy that presents as an acute coronary syndrome without evidence of obstructive atherosclerotic coronary disease. Its name is derived from the Japanese Takotsubo – an octopus trap, resembling the elliptical shape of the very typical akinetic left ventricular apex during systole on imaging studies. It is nowadays increasingly recognized as a new disease entity when faced with normal coronary arteries on angiography with the very typical left ventriculogram, often presenting with acute heart failure, arrhythmias or rarely ventricular rupture.

Case presentation

A 20 previously healthy year old female (including no known drug allergies) presented for an elective breast lumpectomy. After anaesthetic induction, the patient suddenly experienced a twenty second interval of wide complex irregular tachycardia associated with unrecordable blood pressure. The patient was urgently intubated and resuscitated. There was clinical pulmonary edema present. Blood gases revealed metabolic acidosis with severe hypoxia, despite a high oxygen flow rate. An urgent echocardiogram was done which showed ventricular dilatation with apical and anteroseptal hypokinesia. The atria were normal and the base was spared.

Once in the Intensive Care Unit, inotropes and fluids were given to improve blood pressure and oxygen saturation. The patient was kept sedated with 3mg of midazolam and morphine. The electrocardiogram revealed sinus tachycardia with early onset left bundle branch block with absent elevations in creatinine kinase and troponins.

An echocardiogram on the fifth day (after the acute event) showed normal left ventricular dimensions, global and regional contractility with an ejection fraction of 61%. The patient’s parameters eventually normalised and she was discharged home on an angiotensin converting enzyme (ACE) inhibitor and advised to limit physical activity for the next few weeks. A scheduled coronary angiogram was refused by the patient. A review echocardiogram at outpatients was organised at one and three months post-discharge.

Discussion

Aetiology and Pathogenesis

A variety of psychological and physiological stressors (including anaesthesia) have been implicated in the literature, with one study revealing that such precipitants were present in 61% of cases. Two major pathogenic mechanisms have been proposed: a) catecholamine cardiotoxicity as a primary or secondary phenomenon and b) neurogenic stunned myocardium causing epicardial coronary arterial spasm as a result of an exaggerated sympathetic response.

Focal myocytolysis is consistently present in myocardial histology, characteristically absent in myocardial infarction. In addition, biopsies also often display contraction band necrosis, though the catecholamine-mediated myocardial stunning causing the insult is not consistent.

More evidence for an exaggerated sympathetic response has emerged from studies in ovariectomised female rats in which the syndrome of local apical ballooning provoked by restraining stress could be prevented by β-blockade and attenuated by oestrogen suppletion. However, considering the duration of akinesia and the multivessel coronary...
spasm required for such an extensive apical wall abnormality, conventional coronary vasospasm due to sympathetic over-response seems improbable.6

The apical myocardium manifestations could be explained by its high vulnerability towards adrenergic aggression,12 a statement consistent with similar wall abnormalities observed in phaeochromocytoma-related cardiomyopathy.13 However, recently several other forms (Types I-V) of stress-induced cardiomyopathy have been described.14-16

Epidemiologically

The syndrome has a higher preponderance for the female gender in the over sixties, with estrogen possibly playing a role.17,18 Reports in children and young adults have also been reported.19,20 A genetic role might also be possible after an isolated report described the disease in two sisters.21

Clinical Features and Investigations

The patient’s presentations are very non-specific, with sudden onset of symptoms resembling an acute STEMI, with or without cardiogenic shock and arrhythmias.1 The Mayo Clinic have drafted up four major criteria which have to be present in order to diagnose Takotsubo cardiomyopathy.22

Management

The specific treatment of the condition is still largely empirical due to the limited availability of controlled data. Drugs including diuretics, β-blockers such as carvedilol, and ACE inhibitors are often used until recovery of LV function, with no evidence available for their use after recovery. Most importantly, anti-platelets should be considered until a thrombotic pathogenesis is excluded, during the apical akinesis or dyskinesis interval to resolve the cardioembolic risk. Some physicians also consider inotropes or intra-aortic balloon counterpulsation, with the latter being the preferred option due to the potential role of catecholamine excess in the pathogenesis. Follow-up echocardiographic evaluation is routinely performed to ensure resolution of the left ventricular dysfunction and improvement in the ejection fraction.24,25

Prognosis

Although the prognosis for most patients with this syndrome is favorable, with complete recovery of ventricular function within 1 to 4 weeks, several cases of fatal outcomes have been reported.17,26 The evolution, although mainly uneventful, can be complicated, rarely, by left ventricular rupture and ventricular tachycardia, possibly causing sudden death. The recurrence of this syndrome seems to be rare.1

Conclusion

The incidence of “broken heart syndrome” has not as yet been ascertained with the prevalence likely to be under-estimated because of the low level of awareness and infrequent diagnosis. It is nowadays been increasingly recognized in clinical practice which is why more research is needed to determine the exact pathogenesis, increase awareness and optimize management of the syndrome, especially in the acute setting, and identify those subjects prone to this potentially lethal condition.2

References may be accessed at www.thesynapse.net
During August 2-9th 2013, Dr Pierre Vassallo and Ms Kathleen Schembri from DaVinci Hospital will venture to climb the highest mountain in Africa, Mt Kilimanjaro in Tanzania. Kilimanjaro is almost 6000 meters high and reaching the peak is not for the faint hearted.

Successful individuals claim that the ascent is “a killer” particularly the last 1000 meters due to the steepness of the climb and more importantly due to the lack of oxygen. We have prepared ourselves for this task and during the coming months will continue our training to increase our chances. World renowned athletes amongst them Martina Navratilova have failed in their attempts, while less fit individuals who coped better with altitude succeeded. A failure rate of up to 40% of attempts has been reported.

We are fully financing this trip ourselves, however we decided to use the occasion to collect funds to construct a home for disabled children in Ethiopia; this is the Cardinal Van Thuan Home in the province of Jimma. All funds collected through this effort will be channeled towards construction of this home through NGO VO/0140. There will be no deductions made to cover any expenses incurred on our trip.

For information on Cardinal Van Thuan Home please follow this link:
http://www.gesufilproxxmu.com/projects_francis_xavier_cardinal_van_thuan.html
MSc in Reproductive Health

The Department of Obstetrics and Gynaecology of the University of Malta Medical School will in October 2013 be starting a taught part-time 3-year course leading the a Master of Science in Reproductive Health. Entry criteria include only the need for applicants to have an M.D. (Melit.) or its equivalent.

Applications will be eventually posted on the University website.

The course prospectus can be seen at: www.um.edu.mt/ms/obsgynae/noticeboard

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Vaginitis is a common reason for visits to a health care provider, accounting for 6 million visits per year. Symptoms associated with vaginitis can cause substantial distress, resulting in time lost from work and altered self-esteem. It is estimated that over a billion dollars is spent annually on both self-treatment and visits to a medical provider.¹

Normal vaginal flora
Lactobacilli are both the predominant bacteria in the vaginal tract and a regulator of normal vaginal flora. Lactobacilli make lactic acid, which maintains the normal vaginal pH of 3.8 to 4.5, and inhibits the adherence of bacteria to vaginal epithelial cells. Although lactobacilli are the predominant bacteria, other bacteria are also present in the vagina, including streptococcal species, gram-negative bacteria, Gardnerella vaginalis, and anaerobes. Candida albicans can also be found in normal flora as a commensal agent in up to 25% of women.

Pathogenesis of infectious vaginitis
A complex balance of micro-organisms maintains vaginal flora at normal levels. A vaginal infection (infectious vaginitis) occurs when the natural balance of the vaginal flora is disturbed, allowing potentially pathogenic micro-organisms to multiply and prevail.

Infectious vaginitis is accompanied by:
- Signs and symptoms;
- Reduction in the number of lactobacilli;
- Harmful overgrowth of usually present micro-organisms;
- A more or less damaged epithelium.²

Infectious vaginitis may also be caused by exogenous infecting bacteria, fungi, parasites and viruses.³

Candidiasis vs mixed infections
Candidiasis is mostly due to Candida albicans and may be associated with diabetes, pregnancy, recent use of broad-spectrum antibiotics, as well as immunosuppression. Surprisingly, there is no good evidence that tight or synthetic clothing increase the risk of candidiasis. The symptoms are characterised by vulvo-vaginal itch, stinging, burning, external dysuria, and superficial dyspareunia. If a discharge is present it is usually white, cheesy or curd-like. It is estimated that up to 75% of all women will have symptomatic Candida albicans vulvo-vaginitis at some point in their lives.

Recent studies have also suggested that up to 10% of female patients present with mixed candidiasis with two varieties of Candida (C. albicans with C. glabrata is the most common combination, in 86% of cases).⁴ Whereas C. albicans is still the most common fungus isolated in women with recurrent vulvo-vaginal candidiasis, an increased prevalence of non-albicans species, especially C. glabrata, may be found in up to 15% of women with recurrent infections.¹

Management of mixed vaginitis
The management of vaginal discharge is largely syndromic and empirical; it is usually based on naked
The right BALANCE between EFFICACY\(^{(1,2)}\) and RESPECT\(^{(1)}\) for the vaginal ecosystem

POLYGYNAX\(^{®}\) Neomycin sulphate 35 000 IU, polymyxin B sulphate 35 000 IU, nystatin 100 000 IU.

**COMPOSITION:**

- Neomycin sulphate 35 000 IU
- Polymyxin B sulphate 35 000 IU
- Nystatin 100 000 IU

**THERAPEUTIC INDICATIONS:**

Local treatment of vaginitis due to sensitive germs and treatment of non-specific vaginitis. The official recommendations concerning appropriate use of antibacterial products must be taken into consideration.

**POSOLOGY AND METHOD OF ADMINISTRATION:**

For adults only. One vaginal capsule in the evening on an empty stomach for 12 days. Advice: treatment is associated with hygiene recommendations (use cotton underwear, avoid vaginal washing, avoid using a tampon during treatment...). Treatment must be discussed for each individual case. Do not stop the treatment during menstruation period.

**CONTRAINDICATIONS:**

This drug is contraindicated in the following situations: hypersensitivity to one of the components (or relevant group sensitivity). Use of a diaphragm and latex condoms. This treatment is generally not recommended for use with spermicides.

**WARNINGS:**

Treatment should be interrupted in the event of local intolerance or allergic reaction.

**PRECAUTIONS:**

The duration of treatment should be limited because of risk of selecting resistant strains, leading to secondary infection.

**PHARMACODYNAMIC PROPERTIES:**

Local anti-infectious drug (G. genitourinary system and sexual hormones). Combination of neomycin, polymyxin B and nystatin. Neomycin is an aminoside antibiotic. Polymyxin B is a polypeptide antibiotic. Nystatin is a fungicide against Candida.

**SPECIAL STORAGE PRECAUTIONS:**

Store at a temperature not exceeding 25°C.

**PHARMACEUTICAL FORMS AND PRESENTATIONS:**

Box of 6 & 12 vaginal capsules under blister (PVC/Aluminium).

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**LOCAL TREATMENT**

Vaginitis due to sensitive germs and non-specific vaginitis\(^{(3)}\)

1 vaginal capsule in the evening for 12 days

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(3) Summary of product characteristics (SPC) Polygynax® revised in july 2008.
The commonest cause of non-infectious vaginitis is a contact dermatitis from exposure to irritants such as soaps, perfumes, creams as well as atopic dermatitis where persistent scratching may lead to a chronic lichen simplex. Other causes include lichen sclerosus and less commonly lichen planus. Psoriasis may also be the causative agent, as well as premalignant or malignant conditions of the vulva. Pubic lice, scabies, and viral warts are also common causes of vulval itching while hormonal changes, particularly during menopause and breastfeeding may cause atrophic vulvo-vaginitis.

Vulvo-vaginal hygiene

The use of strong soaps, bubble baths and antiseptics around the genital area should be discouraged. ‘Feminine hygiene’ products such as washes, deodorants and powders are rarely appropriate. Vaginal douching in particular is not recommended as it alters the normal vaginal flora and may force bacteria higher into the genital tract.

References

Bibliography
Postgraduate education for healthcare professionals

Every year the University of Malta accepts many students into the Faculty of Medicine and Surgery and the Faculty of Health Sciences, training them to become the healthcare professionals of the future. Tertiary education in the health sciences is traditionally oriented around practical issues, however creativity and individuality may not always be encouraged. This traditional approach results in a workforce that is efficient at solving healthcare problems objectively, but may be rigid with regards to how health professionals use or develop their practical skills. As a pharmacy student, I was exposed to several subjects, but it was neuroscience-based subjects that really struck a chord. Although an unusual and perhaps risky choice, once graduated as a pharmacist, I pursued my academic interest and enrolled in an MSc in neuroscience course at the Institute of Psychiatry, King’s College London. This move was not an easy one, but it was facilitated by a STEPS grant, funded by the Maltese government and the EU Social Fund. The STEPS grants have closed in 2012, but other scholarships such as the MGSS grants are available to financially assist Maltese scholars in their academic ventures, especially those wishing to study abroad and those who have unconventional interests that can benefit Malta.

Applying for grants - and obtaining them - is an important part of furthering one’s academic career and experience. It involves mobilising resources to improve the quality and quantity of a research team’s work, and to effectively demonstrate to the academic community that one’s ideas are promising enough to be worth investing in. In my case, the funding obtained from the STEPS allowed me to follow a taught post-graduate course, as well as to conduct my own original research in pharmacoepidemiology of vascular dementia at the National Institute of Healthcare Research in collaboration with the Institute of Psychiatry (UK). This research allowed me to investigate the risk of mortality associated with antipsychotic use in vascular dementia, the second most common type of dementia. Post-graduate study is rewarding because there is a level of academic maturity among students, and lecturers are able to pass on complex and cutting edge ideas to students who have already mastered the basics in the field. Lecturers and students can - and are expected to - engage in advanced scientific discussion in the lecture room and this type of encounter can lead to future collaborations with senior researchers. Post-graduate study is also rewarding because students are given a degree of freedom in choosing and shaping their own research ideas, when testing the various hypotheses based on their own interests. There is no shortage of opportunities locally or overseas to develop one’s knowledge, and to extend one’s experience in healthcare whilst working with world-class researchers, be it in a purely academic or clinical setting. I encourage all healthcare professionals who feel they’re up to a new challenge to look for post-graduate courses that suit them and apply for grants that can support them in their academic endeavours.
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SUCCESSFUL BUSINESS LUNCHES

When it comes to business there is no better way than doing it over a lunch especially if you’re doing it with people you like.

Business lunches are the most effective way of treating clients, getting to know them closer and making them feel important. Establishing a personal live rapport with your clients is far more effective than any virtual system. So for your business lunch to be successful you will need to plan and dedicate your time as if it was your first date.

These are the steps that work for me whenever I host a business lunch:

- Make sure to select a restaurant that you know. Do not attempt to impress by trying out a new venue.
- Reserve a table in advance and demand it is located in a quiet area. You will need to listen and talk, so disturbances need to be avoided.
- Offer to pick up your client personally. This will not only impress but will give you ample time to conversate on the way. Ensure your car is clean inside out, and keep some mints handy.
- It is important to be in time for the pick up as much as it is to be at the table.
- Get to your menus and place your food orders immediately. This will then leave you more focused on the conversation.
- Avoid ordering meals which are heavy, messy or very demanding to eat. Keep it simple.
- Do not hesitate to make recommendations but leave it to the client to pick the choice.
- If possible get to know beforehand of any religious or cultural beliefs your client might follow, to avoid embarrassing situations with food and drinks.
- Consult with your client before opting for wine and do not put pressure if it is refused.
- Throughout the meal, take care of any requirements personally with the waiting staff.
- Take time to listen and ask questions and show attention. Never gulp in the food leaving your client talking alone.
- Put your mobile phone on silent and exclude any calls that can wait.
- At the end, settle the bill yourself at table and always use a card to pay. This will avoid any attempt to share the bill. Obviously ensure that your card is acceptable.
- Keep in mind that all in all it is the outcome that counts and do not in any way feel too concerned about any mishaps which are out of your control. Even if the client is unsatisfied with the food or service, do not take it personally and do not over-apologise for any shortcomings. The client will always appreciate the fact that you found quality time and gave the relative importance for the business lunch to be successful.

Evento provides professional event organising services to the general public, private or public companies, enterprises, institutions and other organisations requiring a one-stop-shop to their immediate event requests. It also provides consultation, support, over all management, promotional & ancillary services of events to local and foreign markets. Geared up to offer a complete tailor made service, Evento takes a great deal of pride in organising events with innovative concepts and a practical approach.

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The minute I heard Gianluca Bezzina is a doctor, I knew I had to interview him for The Synapse. Doctor... singer... winner of the National Eurovision 2013 Malta Song Contest with a kind of melody that lifts your spirit. Meeting the 23-year-old turns out to be a heart-warming experience.

A newly-graduated doctor, Gianluca is presently a houseman at the St Vincent de Paul Residence for the Elderly. He had been there only a few weeks when he won the song contest – what was that like? “The old ladies on my ward rounds had known about my participation since a few days before the contest. I am a rather shy person and did not talk to anybody about it much, but you know how it is – things get talked about anyhow.”

His win as a soloist threw him in unexpected limelight. Gianluca is indeed not new to singing. A Youth Fellowship member and a Voices choir singer, he is also part of a band - ‘Funk Initiative’ -formed mostly of housemen playing funk and indie, performing regular gigs in several venues. However, his participation in the National Eurovision 2013 Malta Song Contest had nothing to do with his regular band. “My sister, Dorothy Bezzina, who participated in this and in previous editions of the contest, urged me to take part. The song ‘Tomorrow’ was written and composed by Dean Muscat and Boris Cezek who had seen me as a soloist with Voices and urged me to sing for them. ‘Tomorrow’ is our first public song together. On stage I am accompanied by two backing vocals – Louisanne Bugeja Tate and my sister Samaria, the drummer - Christopher Tate, the ukulele player - Kenney D’Ugo and the bassist - Gabriel Cassar. The song, originally meant for radio, is a three-minute-long version prepared specifically for the contest. During the past few weeks we have also released another song called ‘I’ll be There’, together with a new version...
of ‘Tomorrow’ where all my family is singing …”

I realise the doctor has already mentioned two sisters which prompts me to ask about his family. Gianuca’s eyes acquire an added dose of sparkle - “There are seven of us … two girls, three boys and another two girls – 7 kids in 11 years, which makes us a pretty close-knit bunch. I place third, the eldest of the boys. We are a noisy lot, all of us very musical … so there is lots of music constantly playing at home … it can become chaotic at times especially around exam time … but it’s a lively, lovely family of supportive people and I wouldn’t want it any other way. Mum is a primary school teacher (you can understand that she loves children). Dad is an engineer, so we’re all pretty good at sciences”

Which brings us to talk of his studies. “I love medicine, don’t particularly like surgery, am quite interested in geriatrics, but am mad about paediatrics. I feel very inclined to study that further in the future.” He feels he has learnt a great deal through his experience in geriatrics “It’s not just about the amount of medicines and dosages the elderly generally need to ingest… I am impressed by the old people’s personalities… old people are like a closed box of tales and memories which start spilling out as they get to know you. You develop a relationship with the residents and fortunately we have a low turnover rate here which means most of the residents stay here for a long time.” He continues to tell me of his voluntary experiences first with disabled elderly patients at Cotolengo in Italy, and then two experiences with the poor children of Egypt, followed by a stint with the abandoned kids in Palermo. Does he speak Egyptian? “Not at all, but strangely enough, the Egyptians understand Maltese relatively well. Then again you don’t need much to communicate with children – sometimes a smile and a pat on the head is enough.”

“I was initially concerned about how this singing experience would influence my houseman’s reputation at work and my studies … and I had a dilemma concerning how I would cope with the added responsibilities linked to the contest. But I have found a healthy balance and here at work they have all become my fans … so my ‘medical’ image seems to have been salvaged!”

He left for Malmo in Sweden on the 6th of May in preparation for the semi-finals on the 16th and if he proceeds further, the finals on the 18th. How does he feel about this? “Well, I always wanted to go to Sweden, so this is a good opportunity. I like what the contest brings about – the experience. It is also another way to evangelise in my own humble manner. I know people look at the way I speak and the way I behave. I am a super calm, super laid-back persona and whilst I was super excited to be taking part, I had no real expectations and just took on the experience for a buzz. In fact I didn’t even know what I would be wearing on stage before my sister took over and made me decide. Ultimately I want the stage to showcase what I am. I never wanted to compete, never imagined I’d win. Kevin Borg? He’s such a nice fellow. I truly expected him to win. He is such a gentleman, offering me his support in Sweden. We keep in touch on facebook”.

And so the fun continues … all of Malta is now pinning its hopes of a super win in Sweden on this quiet, laid-back but truly charming young singer… will he win, will he not? We can only find out… tomorrow...
IgG4 autoimmune disease (or hyper IgG4 disease) is a relatively recently described systemic disease that is characterised by abundant infiltration of IgG4-positive plasma cells and lymphocytes with associated fibrosis leading to organ dysfunction.

A large number of previously separately known diseases have been found to be associated with increased numbers of IgG4-expressing plasma cells and T lymphocyte infiltration and are now being classified under IgG4 disease. These include orbital inflammatory pseudotumors and Grave’s disease, chronic dacryoadenitis (lacrimal gland inflammation), autoimmune sialadenitis (sjogren’s syndrome), Mikulicz Syndrome, Kuttner’s tumor (fibrosing inflammatory pseudotumor of the salivary glands), Hashimoto’s thyroiditis, Reidel’s sclerosing thyroiditis, bronchiolitis obliterans with organising pneumonia, panniculitis, benign pleural and peritoneal mesothelioma, pleural/peritoneal plaques (including a possible association with asbestos-related diseases), aortitis and autoimmune aortic aneurysms, autoimmune sclerosing cholangitis, autoimmune pancreatitis, retroperitoneal fibrosis and mediastinal fibrosis.

Diagnostic criteria for IgG4-related disease have not yet been established, however any one or more of the following are presently used: (a) characteristic histo-pathologic features, (b) characteristic imaging findings with elevated serum IgG4 levels, and (c) good response to corticosteroid therapy. Multi-organ involvement is the primary indicator that we may be dealing with this autoimmune condition; however multi-organ involvement is also seen in malignant disease particularly lymphoma.

Histo-pathologic analysis of biopsy material shows that IgG4-related disease is characterized by diffuse lymphoplasmacytic infiltration, irregular fibrosis, occasional eosinophilic infiltration, and obliterative vasculitis. Some IgG4-positive plasma cells can be detected in several inflammatory disorders; however, the diffuse infiltration of numerous IgG4-positive plasma cells is characteristic of IgG4-related disease. Serum levels of IgG4 are also elevated and a value 135mg/dL has been claimed as indicative of the condition, however this has not proved to be as accurate as previously suggested.

Since imaging is a primary tool for the diagnosis of IgG4-related disease, the following paragraphs will outline the imaging findings in the more commonly involved organs.

Salivary gland involvement with pathologic conditions such as Mikulicz disease and chronic sclerosing...
sialadenitis (Küttnner tumor) are not uncommon; these are now considered to be part of the spectrum of IgG4-related disease. CT findings of Mikulicz disease include diffuse enlargement of the salivary glands with homogeneous attenuation and homogeneous enhancement with IV contrast administration (Fig 1). MR findings of Mikulicz disease include glandular enlargement with low signal on T2-weighted images (due to high cellular density and a fibrotic component) and homogeneous enhancement similar to that seen on CT (Fig 2). A further characteristic finding of Mikulicz disease is parallel involvement of the lacrimal glands. On the other hand, Küttnner tumor is characterised by a more marked fibrotic component and hence lower signal intensity on T2-weighted sequences; it is also more commonly unilateral than Mikulicz disease.

Lacrimal gland involvement (dacryoadenitis) is most commonly seen in association with salivary gland disease as Mikulicz disease, however isolated and sometimes unilateral lacrimal gland involvement may occur in IgG4-related disease (Fig 3).

Sinus and nasal mucosal involvement may occur with IgG4-related disease. Parallel involvement of other organs particularly the salivary and lacrimal glands help confirm the diagnosis (Fig 4), however biopsy is required when disease is only located at this site. Imaging findings are similar to those seen in the salivary glands with low T2 signal and marked contrast enhancement. Important additional imaging features include absence of bone destruction and perineural extension (along the cranial nerves). The latter feature however is also seen in squamous cell carcinoma, adenoid cystic carcinoma and lymphoma.

An association between Hashimoto’s and Reidel’s thyroiditis and IgG4-related disease has been recently identified. Hashimoto’s thyroiditis is now thought to consist of two subtypes: IgG4 thyroiditis and non-IgG4 thyroiditis. Reidel’s thyroiditis is a systemic IgG4 thyroiditis that is characterised by severe fibrosis that involves all the thyroid and extends beyond the thyroid capsule, which occasionally leads to stridor, requiring tracheostomy. An important imaging feature of IgG-4 thyroid disease is the absence of contrast enhancement on CT and MR (Fig 5), which is in contrast with what is observed in the sino-nasal cavity, salivary glands and orbits.

Hypophysitis is a chronic inflammation of the pituitary gland. There are many causes for hypophysitis that are classified by location or histologic findings; the latter include lymphocytic, granulomatous,
xanthomatous, necrotizing, or IgG4 plasmacytic infiltration (Fig 6).

Lymph node involvement is common in the cervical (Fig 7), mediastinal, hilar, peripancreatic, para-aortic, and mesenteric regions. Lymph nodes generally show low T2 signal on MRI, with homogeneous contrast enhancement on CT and MRI. These findings and also the shape of the involved nodes are however nonspecific, making it difficult to differentiate IgG4-related disease from inflammatory reactive nodes, sarcoidosis, lymphoma, or metastasis.

IgG4-related disease is now noted to be associated with an increasing number of previously known diseases of the chest. Fibrosing mediastinitis is one such condition (Fig 8).

Sclerosing cholangitis, autoimmune pancreatitis, and retroperitoneal fibrosis are increasingly being reported in IgG4-related disease. Concurrent imaging findings of more than one of these entities is particularly helpful in diagnosing IgG4-related disease. Sclerosing cholangitis presents with concentric thickening of bile duct walls (Fig 9) and proximal biliary and pancreatic ductal dilatation (Fig 10). Autoimmune pancreatitis is seen on CT and MRI as diffuse enlargement of the pancreas with a characteristic peripheral rim (Fig 11). Retroperitoneal fibrosis presents as an enhancing soft tissue rim surrounding the aorta (Fig 12), which may extend to a varying degree around its branches and into the surrounding retroperitoneum and may therefore be difficult to distinguish from aortitis.

In conclusion, IgG4-related disease is a recently established, distinct systemic disease that can involve multiple organs and organ systems. This disease responds well to corticosteroid therapy and patients have a good prognosis. Diagnostic imaging helps identify sites of involvement and distribution of the disease. It also helps monitor response to therapy.
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