THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

Volume 17, 2018 Issue 01 ISSN number 2313-8084

Actifed*

Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders [1-7]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [3,6]

Actifed* SYRUP AND TABLETS

- clears blocked and runny noses [2,5]

Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [4,7]

DOSAGE		
LIQUIDS	children aged 2 to 5 years [2-4]	2.5ml every 4-6hrs as required
	children aged 6 to 11 years [2-4]	5ml every 4-6hrs as required
	adults (including the elderly) and children aged 12 years and over [5-7]	10ml every 4-6hrs as required
TABLETS	adults (including the elderly) and children aged 12 years and over [1]	1 tablet every 4-6hrs as required

OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** ACTIFED. **ACTIVE INGREDIENT:** *Actifed DM Cough Linctus:* Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Syrup:* Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Expectorant:* Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg; *Actifed Tablets:* Each tablet contains Pseudoephedrine Hydrochloride 60mg; Triprolidine Hydrochloride 2.5mg. **PHARMACEUTICAL FORM:** Oral Solution and Tablets. **INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of: Actifed DM Linctus: a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; Actifed Expectorant: a nasal decongestant, an anti-histamine and an expectorant; Actifed Tablets: a nasal decongestant, and an anti-histamine. **DOSAGE:** *please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant* are authorised for use without the need of a medical prescription in Adults and Children over 12 years. In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor. **CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of MAOI's in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure. **PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment. **INTERACTIONS:** Sympathomimetics; MAOI's. **ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement. **PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child. **PRESENTATION:** *DM Cough Linctus, Expectorant, Syrup:* Amber glass bottle x 100ml; Tablets: Pack x 24 tablets. Marketing Authorisation Holder: Glaxo Wellcome UK Limited, **Marketing Authorisation Number:** MA 167/00101-7 **Legal category:** POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years. **For further information and full prescribing information contact GlaxoSmithKline (Malta)** Ltd: Tel. 21238131. **Date of preparation:** January 2015

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd(Tel: +356 21238131)

REPORTING ADVERSE EVENTS (AEs): **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

References: 1. Actifed Tablets SPC (Apr 2014); 2. Actifed Syrup SPC (Mar 2015); 3. Actifed DM Cough Linctus SPC (Jan 2015); 4. Actifed Expectorant SPC (Jan 2015); 5. Actifed Syrup SPC OTC (Mar 2015); 6. Actifed DM Cough Linctus SPC OTC (Jan 2015); 7. Actifed Expectorant SPC OTC (Jan 2015)

Job No: MLT_GIB/PDH/0005/16 Date of preparation: February 2016

NIP AND TUCK... EMBRACE THE FUTURE

EDITORIAL

I wish to start 2018 by discussing gene editing which, following last year's remarkable advances, is rumoured to continue to make a star appearance on stage. Gene editing basically rewrites DNA, disabling target genes, correcting harmful mutations and changing the activity of specific genes.

This technology has already been used successfully in the agricultural industry, in that gene editing is faster and more precise than conventional genetic modification, with the added advantage of avoiding the addition of genes from other organisms [this has fuelled the backlash against GM crops]. Seedless tomatoes and gluten-free wheat are some of the results of gene editing.

However, this editorial will discuss the notion of gene editing within the realm of medicine. We have already read about its relation to cystic fibrosis and sickle cell anaemia. However, gene editing has also been recently used to treat infant acute lymphoblastic leukaemia[1] as well as to increase resistance to HIV infection.[2] The cornerstone for this technology is Crispr-Cas9. Crispr stands for '*Clustered Regularly Interspaced Short Palindromic Repeats*' and Cas9 stands for '*Crispr-associated protein-9 nuclease*'. As you may well have envisaged, CRISPR-Cas9 consists of two key molecules. The first component is the Cas9 enzyme. In simple terms, this acts as a pair of 'molecular scissors' that cuts the two strands of DNA at a specific location in the genome so that specific sections of DNA can then be added or removed. The second component is gRNA [guide RNA] which consists of a small piece of pre-designed RNA sequence [approximately 20 bases long] located within a longer RNA scaffold. The scaffold part binds to DNA and the pre-designed sequence 'guides' Cas9 to the right part of the genome. This esnures that the Cas9 enzyme cuts at the right point in the genome. Different enzymes can also be used instead of Cas9, such as Crispr-Cpf1 [*Clustered Regularly Interspaced Short Palindromic Repeats from Prevotella and Francisella 1*].

A question logically crops us … how do the gene editing molecules effectively arrive at the site of action? There are three main methods, viral carriers [lentiviral, adenoviral and adenovirus-associated viral vectors], non-viral carriers [cationic lipid-based vectors] and physical method [electroporation]. These words may seem extracted from a Star Trek episode. However, interestingly, only last year scientists published the results of a proof-of-principle experiment showing that gene-editing [with viral carriers] can effectively be used to prevent muscle wasting in Duchenne muscular dystrophy.[3] Electroporation has, on the other hand, been used to produce micro-holes in embryos to deliver such gene editing molecules ...

More in the next issue…

REFERENCES

1. Qasim W, Zhan H, Samarasinghe S, et al. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. *Sci Transl Med* 2017;9(374).
2. Tebas P, Stein D, Tang WW, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *N Engl J Med* 2014;370(10):901-10.
3. Amoasii L, Long C, Li H, et al. Single-cut genome editing restores dystrophin expression in a new mouse model of muscular dystrophy. *Sci Transl* Med 2017;9(418).

Editor-in-Chief: Dr Wilfred Galea
Managing Editor: Dr Ian C Ellul
Sales & circulation Director: Carmen Cachia

Email: mpl@thesynapse.net
Telephone: +356 21453973/4

Publisher:
Medical Portals Ltd
The Professional Services Centre
Guzi Cutajar Street, Dingli
Malta, Europe

Production: Outlook Coop

Printing: Europrint Ltd

OUR COLLABORATORS

GMMS GERMAN-MALTESE MEDICAL SOCIETY

MMSA

MPSA

MADS Malta Association of Dental Students

The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

Annual subscription rates outside Malta: Six issues €90 or equivalent, worldwide

Imagine a highly disinfected working envornment without the risk of damaging any of your equipment...

12% off on 6 tubs +

Trionic D Spray

The Proven Highly Effective Trionic D concentrate in a convenient Spray-on format

" Ebiox wipes were effective, in less than one minute, in reducing microorganisms to a threshold below which it was not possible to accurately measure their viability "

Independant Test - Q Labs

Disinfection Wipes

Trionic S - For any Washable Surface
Trionic D - For Medical Equipment

PROVEN bactericidal, fungicidal, virucidal and tuberculocidal

Free from alcohol, aldehydes, chlorine, phenols and halogens

ebiox®
advanced decontamination technology

Trade Enquries:

www.jamescotrading.com

JAMESCO
TRADING COMPANY LIMITED
Tel: 21314333

AUTHORS

Dr Michelle Muscat is a speciality registrar in chemical pathology currently in the final stages of her PhD. She previously completed the surgical membership exam and the pathology fellowship exam in clinical biochemistry, as well as a masters degree and a postgraduate diploma.

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 27 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-author of the article is Dr Michael Balzan.

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Health, Malta.

Prof. Albert Cilia-Vincenti MD FRCPath is a surgical pathologist practicing privately. He is a former scientific delegate to the European Medicines Agency, pathology services director to the British and Maltese health services, and a former teacher of London and Malta Universities. He trained at London's Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals.

ISSUE GUIDE

TheSynapse

Augmentin® SR

1000 mg/62,5 mg

Amoxicillin/Clavulanic Acid

Prolonged release tablets

- ✓ Unique bilayer tablet with immediate and sustained release delivery of amoxicillin provides superior efficacy against resistant pathogens[1,2]
- ✓ Recommended by leading Guidelines in the treatment of Community Acquired Pneumonia[3,4]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis[5]
- ✓ Indicated for use in adults & adolescents aged ≥16 years; 2 tablets BD for 7-10 days[5]

Spreading infectious liveliness!

Mini Abridged Prescribing Information: *Please refer to the full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAMES:** Augmentin SR. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATIONS:** Supplied in 28 tablet packs. **INDICATIONS:** Treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae*. **POSOLOGY & ADMINISTRATION:** Oral use. Recommended dose is of two tablets twice daily for seven to ten days. To minimise potential gastrointestinal intolerance, administer at the start of a meal. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Augmentin SR contains 29.3 mg (1.3 mmol) of sodium per tablet. *Refer to the SPC for full list of precautions.* **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥ 1/10): diarrhoea. Common (≥ 1/100, < 1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to the SPC for full list of undesirable effects.* **AUTHORISATION NUMBER:** AA 1051/00102. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** May 2016. **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)** ***REPORTING ADVERSE EVENTS (AEs):*** **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131). ***Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:*** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

References:

1. Benninger MS. Amoxicillin/clavulanate potassium extended release tablets: a new antimicrobial for the treatment of acute bacterial sinusitis and community-acquired pneumonia. Expert Opin Pharmacother. 2003 Oct; 4(10): 1839-46.
2. Anthony R. White *et al.* Augmentin® (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent Journal of Antimicrobial Chemotherapy (2004) 53, Suppl. S1, i3–i20.
3. Gilbert DN, *et al.* Sanford guide to Antimicrobial Therapy v.3.11–last updated March 11, 2014. Sperryville; Antimicrobial Therapy, Inc. 2014 .
4. Mandell LA, Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1; 44 Suppl 2: S27-72.
5. Augmentin SR SPC, April 2015.

Prepared: November 2016 Job No: MLT_GIB/AES/0002/15(3)

For more information and dosing instructions:
www.hcp.gsk.com.mt/products/list/augmentin.html

HOW AND WHY WE AGE: CLINICAL IMPLICATIONS

DR ALFRED GRECH
& DR MICHAEL BALZAN

ABSTRACT

If ageing is perceived as a disease, then there is the potential that we can cure it! But curing ageing entails understanding it. So far, understanding ageing has remained a challenge. However, observations and research, on model organisms and humans alike, are evolving fast. In this review, we will start with a discussion of both the damage and the programmed theories of ageing. Ultimately, we will focus on calorie restriction and telomere shortening and how these relate to lifespan extension.

INTRODUCTION

Someone once said that life should be lived in reverse; die first to get it out of the way, work for forty years until you are young enough to enjoy your retirement, go to school, play, become a little baby, then spend your last nine months floating in the womb. What if, however, instead of living life backwards, we could just slow down ageing and live longer, healthier lives? What if ageing is just a disease that we could cure? So as to answer these questions, we must first attempt to understand the process of ageing, specifically, how and why we age.

THEORIES OF AGEING

In modern gerontology, theories of ageing fall into two main categories: damage (or error) and programmed theories.[1]

DAMAGE (OR ERROR) THEORIES OF AGEING

In 1882, the German biologist Dr August Weismann first introduced the ***wear and tear theory*** of ageing. In essence, his theory states that like components of a car, cells and tissues wear out from repeated use, first killing themselves and then the entire organism. 26 years later, in 1908, Max Rubner postulated the ***rate of living theory***, which states that the faster an organism's metabolism, the shorter its lifespan. Rubner created this hypothesis on observing that larger animals with slower metabolisms outlived smaller ones. In 1928, Raymond Pearl carried out a series of experiments in cantaloupe seeds and the common fruit fly *Drosophila melanogaster* further expanding Rubner's initial observation, i.e. that a slow metabolism increases lifespan. 14 years later, in 1942, Johan Bjorksten proposed the ***cross-linking theory*** of ageing, which states that an accumulation of cross-linked proteins damages cells and tissues, slowing down biological processes resulting in ageing.[2]

In 1956, the ***free radicals theory*** was developed by Dr Harman,[3] where he proposed that free radicals (e.g. superoxide) damage the macromolecular components of the cell; macromolecules (e.g. lipids, nucleic acids, proteins, and sugars) are susceptible to free radical attack. Studies show that reactive oxygen species (ROS) signalling is perhaps the most significant enzyme/gene pathway responsible for cell senescence and organismal ageing. Indeed, ROS signalling is considered as further development of the free radical theory of ageing.[4] Finally, the ***somatic DNA damage theory*** states that DNA damage accumulates with increasing age, causing cells to deteriorate and malfunction. In general, most of the damage is repaired over time, however some accumulates, primarily because the repair mechanisms (e.g. DNA polymerases) do not correct defects as rapidly as they are produced.

PROGRAMMED THEORIES OF AGEING

Three theories fall within this classification. In the ***programmed longevity theory***, ageing is the result of genes switching on and off, with senescence defined as the time when age-associated diseases such as cancer are manifested. In fact, the postulate is that genetic instability is the causing factor of both ageing and cancer. It is therefore legitimate to ask the question whether long-lived individuals actually have a more stable genetic material. Such individuals cannot avoid ageing, but ageing could be postponed due to the stable character of their genome, which is less susceptible to mutations.[5]

In the ***endocrine theory***, biological clocks act through hormones so as to control the rate of ageing. Studies have confirmed that ageing is regulated through hormones, and that the evolutionarily conserved insulin/IGF-1 signalling pathway plays an important part in the hormonal regulation of ageing.[6] Finally, in the ***immunological theory***, the immune system is programmed to weaken with time,

which leads to an increased susceptibility to infectious disease and dysregulated immune responses causing ageing and ultimately death. Indeed, a dysregulated immune response has been indirectly implicated in Alzheimer's disease[7] and cancer,[8] amongst others.

CALORIE RESTRICTION AND ITS IMPLICATIONS

Since the 1930s, it has been found that ***caloric restriction*** (CR) without malnutrition increases lifespan and delays the onset of age-associated diseases in species ranging from yeast to worms to mice to monkeys. For example, at the University of Wisconsin, a few years ago, Colman et al.[9,10] subjected a group of rhesus monkeys of about the same age to CR. CR monkeys ate 30% fewer calories than they ate prior to the start of the study. Over time, it was clear that the monkeys on CR looked younger than those on a normal diet at the same age. Colman et al. also found that the monkeys on the normal diet had 4x greater risk of developing age-associated diseases than those subjected to CR. In addition, brain scans of the CR monkeys, when compared to their well-fed counterparts, showed significantly less atrophy (or cell loss) along the surface of the brain, giving applied insight into Alzheimer's disease. Specifically, this is because the human brain shrinks with normal ageing, but its shrinking doubles in people with Alzheimer's.

It has been discovered that down-regulation of the Ras, Sch9 and Tor pathways mediate part of the effects of CR.[11] Similarly, nutrient sensors termed sirtuins are known to mimic the effects of CR. STACs, or sirtuin-activating compounds, can in theory extend lifespan. In fact, resveratrol and other STACs were found to activate sirtuins and increase lifespan in *Caenorhabditis elegans* and *Drosophila melanogaster,*[12] however their effect on human ageing remains unclear.

Perhaps the best example of CR in humans is that of the Okinawa population. Situated at the southern tip of Japan in the Pacific Ocean, the indigenous Okinawa islanders live for about 110 years on a CR diet. The Okinawa diet is 20% lower in calories than that of an average Japanese. It is rich in anti-oxidants, seafood and vegetables, and it is low in fat and sugar.[13] Okinawans are also active on a daily basis through their traditional practice of martial arts, which also contributes to reduced stress.

TELOMERE SHORTENING AND ITS IMPLICATIONS

Like aglets on shoelaces, telomeres keep chromosome ends from fraying and sticking to each other. In doing so, the genetic material is held intact. It is well-known that each time a cell divides, telomeres shorten. If telomeres get too short and cells are no longer able to divide, senescence occurs. It is this shortening process that is associated with ageing, cancer, and a higher risk of death. Case in point, geneticist Richard Cawthon at the University of Utah established that shorter telomeres are linked to shorter lives.[14] In his study, Cawthon divided people into two groups based on telomere length. Overall, he found that people with longer telomeres live an average of five years more than those with shorter telomeres. Cawthon also showed that people with shorter telomeres are 8x more liable to die from infectious disease and 3x more likely to die from heart disease.

Of note is the disorder known as dyskeratosis congenita where telomeres get short much faster than normal. Some of the manifestations resemble premature ageing (similar to progeria), such as cirrhosis of the liver, a higher risk of infections, intestinal disorders, leukaemia and other blood cancers, and pulmonary fibrosis. In addition, patients are more prone to endure balding, grey hair, and softening of the bones. However, the main consequence of the disorder is progressive bone marrow failure, causing early mortality.[15] With all this, one is lead to presume that restoring telomere length could treat ageing and/or age-associated disorders. Professor Elizabeth Blackburn, who was awarded the Nobel Prize in Physiology or Medicine in 2009, co-discovered telomerase, an enzyme that halts telomere shortening and can even lengthen them.[16,17] For this reason, after its discovery, telomerase was reputed to be the new fountain of youth, as evidenced in Jaskelioff et al.'s experiment.[18] Jaskelioff et al. showed that mice that are engineered to lack telomerase become prematurely old, whereas when the enzyme is replenished, the mice's health is restored.

Similarly, scientists have exploited telomerase in the lab to keep human cells dividing beyond their normal, or Hayflick, limit without allowing them to become cancerous. In general, the implications for this are wide. If telomerase were to be used to "immortalise" human cells, we would then be able to mass-produce cells for transplantation, including cartilage cells for curing arthritis, insulin-generating cells for diabetes, muscle cells for muscular dystrophy, and skin cells for treating burns and wounds. In addition, having a limitless source of human cells could also help with efforts to test new drugs and gene therapies.

CONCLUSION

Overall, understanding the causal processes that deteriorate with age is critical if we are to meet the growing healthcare requirements of ageing human populations. However, this is not a straightforward task; ethical and societal implications of ageing research should also be taken into consideration. For example, how would treating human ageing affect society? What should the ultimate goals of ageing research be?

REFERENCES

1. Jin K. Modern Biological Theories of Aging. *Aging and Disease* 2010;1(2):72-74.
2. Bjorksten J, H Tenhu. The Crosslinking Theory of Aging - Added Evidence. *Experimental Gerontology* 1990;25(2):91-95.
3. Harman D. Aging: a Theory Based on Free Radical and Radiation Chemistry. *The Journals of Gerontology* 1956;11(3):298-300.
4. Afanas'ev I. Signaling and Damaging Functions of Free Radicals in Aging-Free Radical Theory, Hormesis, and TOR. *Aging and Disease* 2010;1(2):75-88.
5. Davidovic M, Sevo G, Svorcan P, et al. Old Age as a Privilege of the "Selfish Ones". *Aging and Disease* 2010;1(2):139-146.
6. van Heemst, D. Insulin, IGF-1 and Longevity. *Aging and Disease* 2010;1(2):147-57.
7. Rozemuller AJ, van Gool WA, Eikelenboom P. The Neuroinflammatory Response in Plaques and Amyloid Angiopathy in Alzheimer's Disease: Therapeutic Implications. *Current Drug Targets - CNS and Neurological Disorders* 2005;4(3):223-33.
8. Foster AD, Sivarapatna A, Gress RE. The Aging Immune System and its Relationship with Cancer. *Aging Health* 2011;7(5):707-718.
9. Colman RJ, Anderson RM, Johnson SC, et al. Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys. *Science* 2009;325(5937):201-204.
10. Colman RJ, Beasley TM, Kemnitz JW, et al. Caloric Restriction Reduces Age-Related and All-Cause Mortality in Rhesus Monkeys. *Nature Communications* 2014;5:3557.
11. Wei M, Fabrizio P, Hu J, et al., Life Span Extension by Calorie Restriction Depends on Rim15 and Transcription Factors Downstream of Ras/PKA, Tor, and Sch9. *PLoS Genetics* 20084(1):e13.
12. Wood JG, Rogina B, Lavu S, et al. Sirtuin Activators Mimic Caloric Restriction and Delay Ageing in Metazoans. *Nature* 2004;430(7000):686-689.
13. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric Restriction, the Traditional Okinawan Diet, and Healthy Aging: the Diet of the World's Longest-Lived People and its Potential Impact on Morbidity and Life Span. *Ann N Y Acad Sci* 2007;1114:434-455.
14. Cawthon RM, Smith KR, O'Brien E, et al. Association between Telomere Length in Blood and Mortality in People Aged 60 Years or Older. *Lancet* 2003;361(9355):393-395.
15. Bessler M, Du HY, Gu B, et al. Dysfunctional Telomeres and Dyskeratosis Congenita. *Haematologica* 2007;92(8):1009-1012.
16. Blackburn EH. Telomeres and Tetrahymena: an Interview with Elizabeth Blackburn. *Disease Models and Mechanisms* 2009;2(11-12):534-537.
17. Greider CW, Blackburn EH. A Telomeric Sequence in the RNA of Tetrahymena Telomerase Required for Telomere Repeat Synthesis. *Nature* 1989;337(6205):331-337.
18. Jaskelioff M, Muller FL, Paik J, et al. Telomerase Reactivation Reverses Tissue Degeneration in Aged Telomerase-Deficient Mice. *Nature* 2011;469(7328):102-106.

ACTIVATE THE HEART*

ACTIVATE LIFE[1,2]

GUIDELINE† CLASS I RECOMMENDED[3,4]

Change your symptomatic HFrEF patients to ENTRESTO®

- **Activates the heart's beneficial response** by enhancing the natriuretic peptide system, while maintaining RAAS inhibition[5,6]
- **20% reduced risk** of CV death or first heart failure hospitalisation vs enalapril ($P<0.0001$; ARR=4.7%)[5‡]
- **Significant improvements in Quality of Life** vs enalapril, as measured by reduced deterioration of heart failure symptoms and physical limitations ($P=0.001$)[7§]

When you see symptoms, IT'S TIME FOR ENTRESTO[5]

Entresto®
sacubitril/valsartan

ARR=absolute risk reduction; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; RAAS=renin-angiotensin-aldosterone system.

*The complementary cardiovascular benefits of ENTRESTO in patients with HFrEF are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitril and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan.

† Based on 2016 ESC HF Guidelines and 2017 ACC/AHA/HFSA Guideline Update.

‡ Primary end point.

§ Secondary end point that measured the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

ENTRESTO™▼(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). Indications: 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. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing 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 Entresto 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 Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is 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 Entresto is not recommended. Use of Entresto 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. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto 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 of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto 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 (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto 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 Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto 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 Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto 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 Entresto 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 Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto 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 Entresto 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 Entresto 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; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Frimley Business Park, Camberley, GU167SR, United Kingdom. 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. 2016-MT-ENT-16-JUN-2016

References: 1. Fala L. Entresto (sacubitril/valsartan): first-in-class angiotensin receptor neprilysin inhibitor FDA approved for patients with heart failure. *Am Health Drug Benefits*. 2015;8(6):330-334. 2. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci*. 2016;130(2): 57-77. 3. Ponikowski P, Voors A, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200. 4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017; 136(6):e137-e161. Epub 2017 Apr 28† 5. ENTRESTO Core Data Sheet, version 1.1. Novartis Pharmaceuticals. August 2015. 6. McMurray JJV, Packer M, Desai AS, et al. Dual Angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure. *Eur J Heart Fail*. 2013;15(9):1062-1073. 7. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

NOVARTIS

ENT Ad1 01/18 MT

IS LYMPHOMA CURABLE?

SHORT ACCOUNTS OF INTERESTING CASES, SOME MEDICAL DISASTERS, INVOLVING PATHOLOGY AND CLINICAL PRACTICE, FROM THE RECOLLECTION OF PROF. ALBERT CILIA-VINCENTI.

This is early 1980s, a few years after I took up a consultant surgical pathologist post at the Royal Hampshire County Hospital in Winchester. I get a call from Dr Anthony Galea-Debono who is now a physician and neurologist in private practice in Malta. In the late 1970s, Tony and I used to meet often over lunch because we worked not far from each other in London, him at Queen's Square and I at The Middlesex in Mortimer Street.

The call from Galea-Debono is about a young woman in her early thirties who has been referred to him for management of a diagnosis of tuberculosis following an excision biopsy of an enlarged neck lymph node, and wishes the histology reviewed before he starts anti-tuberculous therapy. The lymph node histology, in fact, shows what I thought was a high grade large cell lymphoma with necrosis, the latter feature having been misinterpreted as tuberculous necrosis. The patient also complained of retrosternal pain on ingesting alcohol. I confirm the lymphoma diagnosis with Professor Dennis Wright, at the time a world figure in lymphoid pathology, and conveniently located in Southampton, just down the road from Winchester.

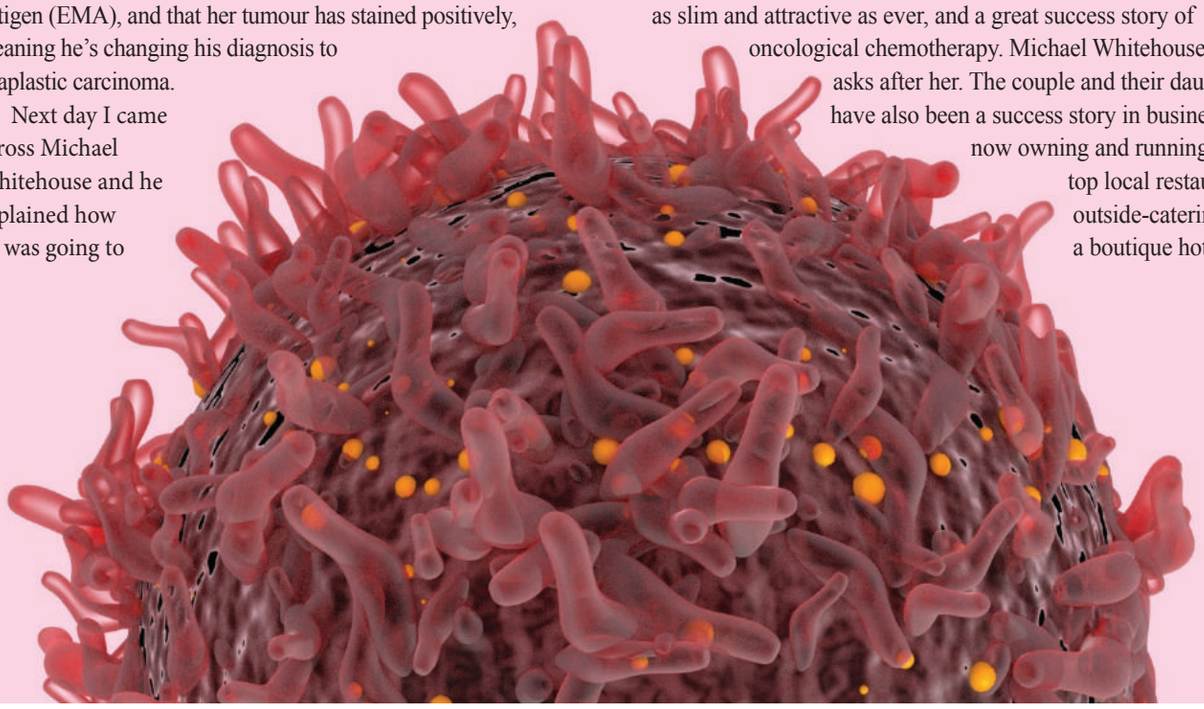
Galea-Debono says that the patient wishes to come up to UK to consult an oncologist and I recommend Professor Michael Whitehouse in Southampton, a jovial, moral-lifting doctor with great bed-side manner. The patient and her husband leave immediately for Southampton. By the time they get to UK, Dennis Wright has rung me to announce that his laboratory has tried their first immunohistochemistry diagnostic technique on this patient's lymph node using an antibody to epithelial membrane antigen (EMA), and that her tumour has stained positively, meaning he's changing his diagnosis to anaplastic carcinoma.

Next day I came across Michael Whitehouse and he explained how he was going to tackle the problem of two diagnoses, high grade lymphoma and anaplastic carcinoma. As no treatment regime existed for anaplastic carcinoma, he was going to try high grade lymphoma therapy in case it worked. He explained to the patient that she had a one in four chance of cure. She was given her first course of combination chemotherapy in Southampton, her hair fell out and returned to Malta with a suitable wig and with chemotherapy regime instructions for Galea-Debono to follow.

Back in Malta, the doctors' strike was still part of the medical services scene and Galea-Debono, probably assisted by oncologist Dr Victor Muscat, oversaw the completion of the patient's chemotherapy regime. I remember some feedback that the Southampton chemotherapy dosages were significantly higher than they had ever used in Malta. The patient did manage to complete the treatment course and her hair grew back. The couple had two small girls and they were struggling to set up a business.

Five years later the patient was fit and well, so I sent her lymph node paraffin block back to Dennis Wright to review his diagnosis of anaplastic carcinoma. Five years was a long time in evolution of immunohistochemistry and with newer antibodies to various diagnostic antigens, Dennis Wright now diagnosed a T-cell high grade lymphoma. We now know that some lymphomas stain positively with an epithelial membrane antigen antibody – this is only one of the many pitfalls in diagnostic immunohistochemistry interpretation. If Michael Whitehouse had not ignored immunohistochemical misinterpretation of anaplastic carcinoma, this patient would not have survived.

Almost 35 years later, this patient is a picture of health, as slim and attractive as ever, and a great success story of oncological chemotherapy. Michael Whitehouse always asks after her. The couple and their daughters have also been a success story in business, now owning and running three top local restaurants, outside-catering and a boutique hotel.



WITH ULTIBRO® BREEZHALER®
EXACERBATION PREVENTION IS IN YOUR HANDS[1]

ULTIBRO® BREEZHALER® is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)[2]

FLAME STUDY RESULTS[1]

"...[ULTIBRO® BREEZHALER®] showed not only non-inferiority, but also... consistent superiority to [Seretide®* Accuhaler®] for all outcomes related to exacerbations, lung function† and health status**.[1‡§]"

The FLAME study is a 52-week head-to-head trial comparing ULTIBRO® BREEZHALER® with Seretide® Accuhaler® (LABA/ICS) in 3362 exacerbating‡ COPD patients.[1] The primary endpoint was to demonstrate that ULTIBRO® BREEZHALER® was at least non-inferior to Seretide® Accuhaler® in reduction of all exacerbations. Superiority over Seretide® Accuhaler® was a pre-defined secondary endpoint.[1]

*Fluticasone/salmeterol 500/50 mg BID. †Lung function trough FEV, (P<0.001).[1] **Health-related quality of life, SGRQ-C (P<0.01).[1] ‡Patients had at least one moderate or severe exacerbation in the previous 12 months.[1] §Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 11% (RR 0.89, P=0.003). Annual rate reduction of moderate or severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 17% (RR 0.83, P<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 13% (RR 0.87, P=0.23).[1] Seretide® Accuhaler® is a registered trademark by GSK.

BID, twice daily; COPD, chronic obstructive pulmonary disease.

ONCE DAILY
ultibro® breezhaler®
indacaterol maleate/glycopyrronium bromide
inhalation powder

Ultibro Breezhaler inhalation powder, hard capsules

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION: Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. **Method of administration** For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. ***Asthma:*** Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. *Paradoxical bronchospasm:* As with other inhalation therapy, administration of Ultibro Breezhaler may result in paradoxical bronchospasm which can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. Narrow-angle glaucoma: No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. Urinary retention: No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, dyspepsia, dental caries, bladder obstruction and urinary retention,, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, , gastroenteritis tachycardia, palpitations, , insomnia Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:**POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003 , EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872

2016-MT-ULT-10-NOV-2016

References

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

NOVARTIS

ULT Ad1 01/18 MT

DR MICHELLE MUSCAT

GENETIC ENGINEERING, SCIENCE FICTION AND ENVIRONMENTAL TOXICOLOGY IN A MANGA: ‘COPPELION’

MANGA
Author: Tomonori Inoue **Publisher:** Kodansha
Magazine: Monthly Young Magazine **Run:** 2008 – 2016

ANIME TV SERIES
Director: Shingo Suzuki **Writer:** Mokoto Nakamura
Run: October - December 2013

Various radioactivity alertness programmes and strategies have been developed. These encompass both the medical countermeasures subsequent to radiation exposure as well as longer term plans for bioremediation. ‘Coppelion’ provides a compelling glimpse at the wasteland left after a nuclear disaster and a peculiar new concept, namely that of the radiation-immune genetically engineered human.

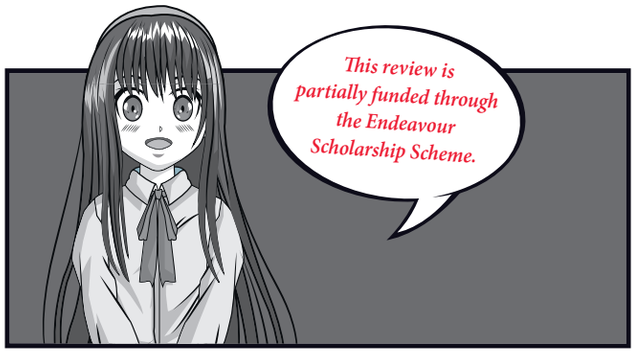
Before delving into the fictional universe of ‘Coppelion’, it is worthy to note some relevant real life instances. In the wake of past nuclear disasters which led to large-scale release of radioactivity such as the notorious Chernobyl disaster back in 1986, and more recently, the Fukushima Daiichi nuclear disaster in 2011, Belgium had announced precautionary measures as part of a nuclear emergency plan, which included providing the whole population with iodine tablets. Medical countermeasures to radioactive exposure include use of potassium iodide, prussian blue, DTPA (diethylenetriamine pentaacetate) and filgrastim.[1-7]

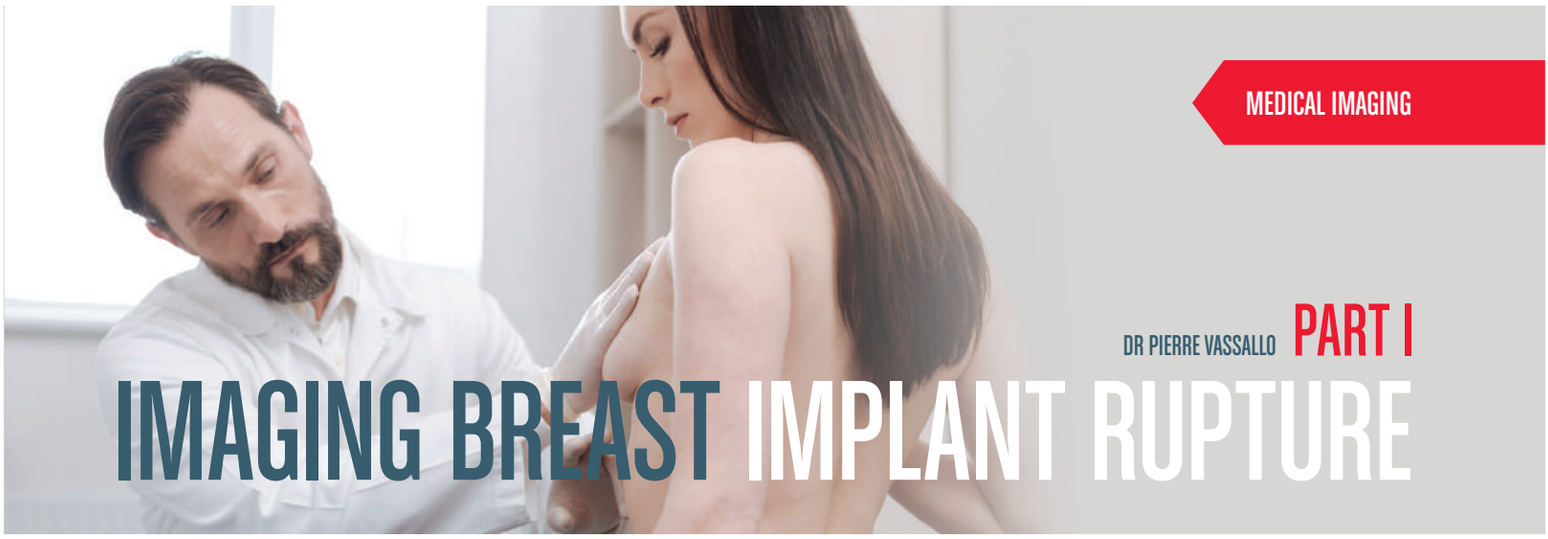
In the science fiction world of ‘Coppelion’ we are initially presented with three genetically engineered girls forming the medical unit Coppelion, after a large scale nuclear meltdown. Concepts of environmental toxicology are central to the plot progression and in various instances the viewer is presented with issues of waste disposal, such as waste being dumped in the wasteland of the nuclear incident; and at one point one of the girls is treated with hyperbaric oxygen. ‘Coppelion’ anime television series was based on a *seinen* manga by the same name, written by Tomonori Inoue and published by Kodansha from 2008-2016. The story of ‘Coppelion’ plays heavily on the elements of science fiction, namely rendering the teenage girl protagonists immune to the nuclear radiation and hence able to roam freely amongst the ruins without requiring personal protective gear.

In a classical comic ballet which premiered in 1870 and bearing a similar name, namely ‘Coppélia’, Dr Coppélius creates a life-sized doll. The life-sized doll or ‘puppet’ parallels are felt in the Coppelion story, which in turn give rise to ethically-charged questions with respect to the subjecting of these girls to genetic modification. The lead girl, Ibara Naruse, however, still retains hope and a positive outlook, in the inhospitable surroundings and challenging situations.

In practice, many biotechnology techniques have been put forth in an attempt to help decontaminate soil, such as for example, the use of immobilized photosynthetic bacteria coupled with anaerobic digestion and fermentation of lactic acid.[8] Scavenging-precipitation ion exchange methods[9] form part of the growing initiative in ecotoxicology for bioremediation.[10] There are both severe acute and long term consequences to health arising from the dispersion of radioactive material,[11, 12] hence viewing ‘Coppelion’ is both entertaining and topical.

REFERENCES
1. Breeman WA, De Jong MT, De Blois E, Bernard BF, De Jong M, Krenning EP. Reduction of skeletal accumulation of radioactivity by co-injection of DTPA in [90Y-DOTA0,Tyr3]octreotide solutions containing free 90Y3+. Nuclear medicine and biology. 2004;31(6):821-4.
2. Kitajima A, Ogawa H, Kobayashi T et al. Monitoring low-radioactivity caesium in Fukushima waters. Environmental science Processes & impacts. 2014;16(1):28-32.
3. Kunii Y, Uruno T, Mukasa K et al. Inhibitory effect of low-dose inorganic iodine on thyroidal radioactive iodine uptake in healthy Japanese adults. Endocr J. 2016;63(1):21-7.
4. Verger P, Aurengo A, Geoffroy B, Le Guen B. Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. Thyroid : official journal of the American Thyroid Association. 2001;11(4):353-60.
5. Zanzonico PB, Becker DV. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by 131I from radioactive fallout. Health physics. 2000;78(6):660-7.
6. MacVittie TJ, Bennett AW, Farese AM et al. The Effect of Radiation Dose and Variation in Neupogen(R) Initiation Schedule on the Mitigation of Myelosuppression during the Concomitant GI-ARS and H-ARS in a Nonhuman Primate Model of High-dose Exposure with Marrow Sparing. Health physics. 2015;109(5):427-39.
7. Did you know? Prussian blue dye. Consumer reports. 2004;69(1):45.
8. Sasaki K, Morikawa H, Kishibe T et al. Practical removal of radioactivity from soil in Fukushima using immobilized photosynthetic bacteria combined with anaerobic digestion and lactic acid fermentation as pre-treatment. Biosci Biotechnol Biochem. 2012;76(9):1809-14.
9. Brooksbank RE, Browder FN, Holcomb RR, Whitson WR. Low-Radioactivity-Level Waste Treatment. Ii. Pilot Plant Demonstration of the Removal of Activity from Low-Level Process Wastes by a Scavenging-Precipitation Ion-Exchange Process. Ornl-3349. ORINS [reports] US Atomic Energy Commission. 1963;86:1-63.
10. Luo X, Zeng XC, He Z et al. Isolation and characterization of a radiation-resistant bacterium from Taklamakan Desert showing potent ability to accumulate Lead (II) and considerable potential for bioremediation of radioactive wastes. Ecotoxicology. 2014;23(10):1915-21.
11. Thiessen KM, Andersson KG, Batandjieva B et al. Modelling the long-term consequences of a hypothetical dispersal of radioactivity in an urban area including remediation alternatives. Journal of environmental radioactivity. 2009;100(6):445-55.
12. Jonsson L, Plamboeck AH, Johansson E, Waldenvik M. Various consequences regarding hypothetical dispersion of airborne radioactivity in a city center. Journal of environmental radioactivity. 2013;116:99-113.





MEDICAL IMAGING

DR PIERRE VASSALLO

PART I

IMAGING BREAST IMPLANT RUPTURE

Breast augmentation is the most common form of cosmetic surgery performed today. Most procedures involve the insertion of silicone gel-filled prostheses, which are selected for size and contour based on the woman's body habitus and preference.

The first gel-filled breast implants were developed in the early 1960's, however these suffered from high material failure rates and were initially thought to be linked to connective tissue disorders. Major redesigns and material improvements have lead to the development of 4th and 5th generation implants that have semi-solid silicone filler-gel and a strong silicone capsule. These new implants have the advantage of retaining their original shape and have a lower risk for rupture.

Implant rupture is the most common complication of silicone breast implantation and is more likely to occur with increasing implant age. This is due to weakening of the implant shell; the mean implant life span has been reported to be 13 years.[1]

Due to its semi-solid consistency, rupture of a silicone-filled implant may cause no symptoms and may be incidentally noticed during breast imaging studies. This contrasts with rupture of water-filled implants, which deflate rapidly producing a dramatic change in breast shape. Clinical findings of silicone breast implant rupture, when present, may include changes in breast size or shape, a palpable abnormality in the breast or axilla, pain, or skin tightening.[2]

Mammography does not cause implant rupture; anecdotal cases of this occurrence are likely due to implant leak that occurred prior to the mammographic examination.[3]

A fibrous capsule forms around the implant's shell; this represents the body's attempt to wall itself off from the foreign

object; this fibrous capsule creates a barrier that has important implications in limiting flow of free silicone in case of implant rupture. A rupture that involves the implant shell with an intact fibrous capsule is called an intracapsular rupture (Fig 1b), while breakdown of the fibrous capsule with extravasation of silicone into the adjacent tissues is known as an extracapsular rupture (Fig 1c). Around 85% of implant ruptures are of the intracapsular type and most will cause no clinical symptoms or signs. Extension of silicone outside the capsule may induce an inflammatory response that may cause pain and local deformity.

Diagnosis of implant rupture with mammography, ultrasound and Magnetic Resonance Imaging (MRI) has been described in several articles; the advantages of each imaging modality will be discussed below.

MAMMOGRAPHY

Mammography is the least sensitive breast imaging modality for implant rupture. This results from the high density of silicone that prevents internal analysis of the implant. However, evaluation of the contours of a breast implant may indicate a problem with implant integrity (Fig 2a); it is particularly useful to compare with previous exams when analysing changes in implant contour.

Intracapsular tears are mostly missed by mammography. A rounded implant shape may indicate capsular contracture but does not indicated rupture. Calcifications within the capsule occur with older long-standing implants and are not indicative of rupture.

Mammography is useful for detecting an extracapsular rupture since there is extravasation of silicone into the surrounding breast tissue (Fig 3). However, careful attention must be given in the case of a replaced implant, since free silicone will persist within the soft tissues from a previous implant leak. An extracapsular leak may result in silicone collecting within the axillary lymph nodes. However, small amounts of silicone in axillary lymph nodes may result from a process known as "gel-bleed" and are not a sign of implant rupture; gel-bleeds occur when freed silicone molecules that were not fully bound within the polymer capsule leak into surrounding tissues and are transported to regional lymph nodes.

The primary purpose of mammography is to screen for breast cancer; it should not be used to detect implant rupture.

To be continued…

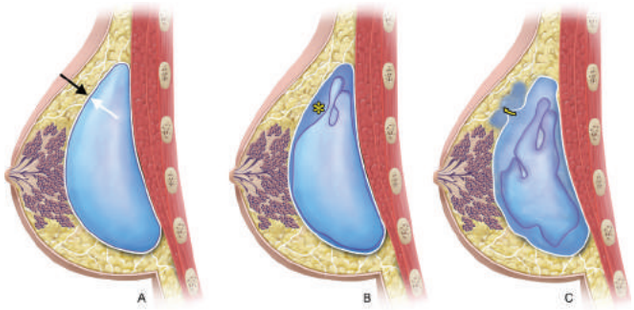


Figure 1: A. Intact implant showing capsule (black arrow) and implant shell (white arrow). **B.** intracapsular rupture with silicone (*) present between the capsule and the shell. **C.** extracapsular rupture with silicone extravasating (arrow) outside the capsule.

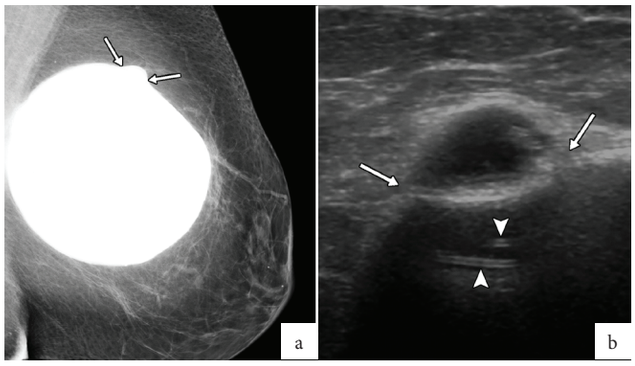


Figure 2: A. Mammogram showing an abnormal implant contour (arrows). **B.** Ultrasound confirms an intracapsular rupture with silicone leak (arrows) and a displaced shell depicted as parallel echogenic lines (arrowheads).

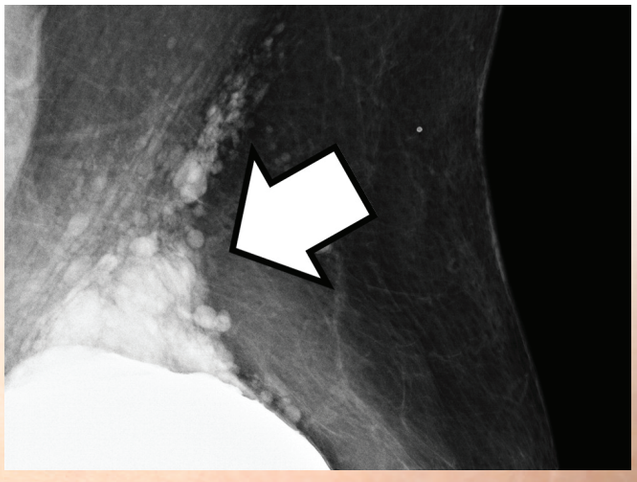


Figure 3: Extravasation of silicone into breast tissue (arrow) confirming an extracapsular implant leak.

REFERENCES

1. Rohrich RJ, Adams WP Jr, Beran SJ, et al. An analysis of silicone gel-filled breast implants: diagnosis and failure rates. Plast Reconstr Surg 1998;102(7):2304–2308; discussion 2309.
2. Hölmich LR, Fryzek JP, Kjøller K, et al. The diagnosis of silicone breast-implant rupture: clinical findings compared with findings at magnetic resonance imaging. Ann Plast Surg 2005;54(6):583–589.
3. Juanpere S, Perez E, Huc O, et al. Imaging of breast implants: a pictorial review. Insights Imaging 2011;2(6):653–670.

Serotonergic antidepressants **insufficiently** address the core depressive symptoms associated with "Decreased positive affect"[1]

Loss of pleasure, Loss of interest, Fatigue, Loss of energy

Wellbutrin XR should not be used together with other Bupropion containing medicinal products.
Wellbutrin XR tablets should be swallowed whole and not crushed or chewed.

WELLBUTRIN XR – Abbreviated Prescribing Information: ***Please refer to full Summary of Product Characteristics (SmPC) before prescribing.*** **TRADE NAME:** Wellbutrin XR modified release tablets. **COMPOSITION:** Buproprion Hydrochloride 150mg and 300mg. **INDICATIONS:** Treatment of major depressive episodes. **POSOLOGY AND METHOD OF ADMINISTRATION:** Wellbutrin XR tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse events including seizures. *Adults:* The recommended starting dose is 150mg once daily; if no improvement is seen after 4 weeks the dose may be increased to 300mg once daily. There should be an interval of at least 24 hours between successive doses. *Children and Adolescents:* Not indicated for use in children or adolescents aged less than 18 years. *Elderly Patients:* Same as adults but with greater sensitivity in some elderly individuals. *Hepatic and renal impairment:* 150mg once a day. *Discontinuing therapy:* A tapering off period may be considered. *Overdose:* Symptoms including drowsiness, loss of consciousness and/or ECG changes and rarely deaths even with large overdoses. **CONTRAINDICATIONS:** Hypersensitivity to buproprion or any of the excipients; co-administration with other medicinal products containing buproprion as the incidence of seizures is dose-dependent; current seizure disorder or history of seizures; known CNS tumor; withdrawal from alcohol or any medicinal product known to be associated with the risk of seizures on withdrawal; severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **SPECIAL WARNINGS AND PRECAUTIONS:** Do not exceed the recommended dose of Wellbutrin XR especially in patients who have predisposing factors for seizures since the risk of seizures is dose-related. Not recommended/discontinued in patients who experience a seizure during treatment. Careful monitoring during the first weeks of treatment/dose changes/in patients with history of suicide-related events prior to treatment; discontinuation should be considered in cases of severe and sudden onset of suicidal ideation/behaviour. Wellbutrin XR should be discontinued promptly if patients experience hypersensitivity reactions during treatment; Use with caution in patients with hepatic and renal impairment. **INTERACTIONS:** Concomitant use with MAOI's is contraindicated; The dose of certain antidepressants, anti-psychotics, beta-blockers, SSRI's and Type 1C antiarrhythmics should be reduced when given concomitantly with Wellbutrin XR; Use with caution with cyclophosphamide and ticlopidine, carbamezapine, phenytoin, ritonavir, tamoxifen, valproate, levodopa or amantidine, alcohol and nicotine transdermal system. **ADVERSE EVENTS:** *Very Common:* Insomnia, headache, dry mouth, gastrointestinal disturbance including nausea and vomiting; *Common:* Hypersensitivity reactions such as urticaria, anorexia, agitation, anxiety, tremor, dizziness, taste disorders, visual disturbance, tinnitus, increased blood pressure (sometimes severe), flushing, abdominal pain, constipation, rash, pruritus, sweating, fever, chest pain and asthenia. *Not known:* suicidal ideation and suicidal behaviour. Refer to the SPC for a full list of adverse events. **PREGNANCY AND LACTATION:** Not recommended. **ABILITY TO DRIVE AND USE MACHINES:** Use with caution. **PRESENTATIONS:** Wellbutrin XR 150mg and 300mg x 30 tablets. **LEGAL CATEGORY:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, UK. **Marketing Authorisation Number:** MA 302/00101-2. **Date of preparation:** August 2016

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)

REPORTING ADVERSE EVENTS (AEs):

If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal

Put depression behind them.

References: 1. Nutt DJ, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, *et al.* The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. J Psychopharmacol 2007; 21: 461–471.

Job No: MLT_GIB/BHC/0002/16a Prepared: October 2016

For more information
www.hcp.gsk.com.mt/products/list/wellbutrin.html

Wellbutrin® bupropion hydrochloride XR

The Noradrenaline & Dopamine Re-uptake Inhibitor.

A DOCTOR, HIS PATIENTS AND MINIATURE TREES

Marika Azzopardi meets **Dr Alfred Grech** for an insight on the daily work of a GP and the life of miniature trees.

TS: WHAT CAN YOU TELL ME ABOUT YOUR CAREER AS A DOCTOR?

I graduated in 1985. Over the years I experienced several different aspects of being a GP and family doctor. For instance, I was, for a substantial amount of time, one of the doctors responsible for the Malta Drydock employees in the south of Malta, visiting them at home when they were on sick leave. I also had my private clinic, serving families in Kirkop which is my hometown, as well as Safi and Luqa. Eventually, two years ago, after several years working also at the Paola Health Centre, I opted for Contract A. In order to conform with the conditions of this contract, similarly to other doctors working in health centres around Malta, I had to terminate my private practice and now work solely at the Paola Health Centre. It was very difficult letting go of my private practice because I miss the aspect of patient continuity of care. I actually felt bad telling my patients I was closing my clinic. Many of my patients knew me on a first name basis since I had taken care of their health and that of their family for many years. On another note however, this change in work schedule has also changed my work rhythms and given me a new lease of life with so much more free time to spend with my family and doing what I love best...

TS: WHAT CAN YOU TELL ME ABOUT YOUR PRESENT ROLE?

I am presently Principal General Practitioner (PGP), sharing the workload with another PGP here. At times, duties are mostly management-oriented. A case in point is the allocation of all the doctors in the centre, when the other PGP is on leave, creating a daily roster to fit around the needs of this busy health centre. We are all preparing for the eventual new Paola Health Centre which will be a state-of-the-art health hub at the site of the former Schreiber ground.

TS: SPEAKING OF DOCTORS, ESPECIALLY YOUNG DOCTORS, WHAT CHANGES HAVE YOU WITNESSED OVER THE YEARS, REGARDING THEIR FORMATION?

In my case, after emerging from university I had three months' experience in dermatology, three months' experience in surgery, three months in medicine and another three in psychiatry.

At 'Notre Dame Bonsai Garden', Floriana during the 25th Annual Bonsai Exhibition 2016 (4th-5th June) with my 7-tree forest. All exhibited trees were grown over the years from small cuttings and potted at home in hand-made pots. Two weeks before the show I defoliated the trees to allow a better visual of all the trees and their ramification over the years, leaving enough time for new small leaves to emerge to add some green.

Delivering a presentation on how to cultivate a bougainvillea as a bonsai at the Bonsai Culture Group-Malta clubhouse in Floriana.

At the Bonsai Culture Group-Malta's annual Bonsai exhibition with my two daughters and my first bonsai tree – a sandarac gum tree (the national Maltese Gharghar tree) grown from seed.

That was it. After that, I was allocated to Paola Health Centre. I still remember my perplexity with skin rashes. For example, prior to my commencent at the health cantre, I had never seen chickenpox manifested on anybody. I quickly learnt after observing a seasoned doctor diagnose spots on a child as being chickenpox. Before that, I had absolutely no clue what the spots indicated. Today things are so much different and much better for new doctors who can consult their assigned mentors for guidance when in doubt.

TS: CAN YOU IDENTIFY SOME CASES WHICH TOUCHED YOU OVER THE YEARS?

Personally speaking, the most impressive cases which left me considerably distressed were suicide cases and stories of gross neglect as in the case of the very elderly. As a young doctor, you receive a call and you have to go in and deal with horrendously difficult human stories which touch you to the core. We never had counselling to help us overcome such experiences. I very much doubt whether new doctors are given any such psychological assistance even today.

TS: WERE YOU EVER TEMPTED TO TRAIN FURTHER AND SPECIALISE?

No. I was content with becoming a family doctor and GP. But today, in hindsight, I know that, given a second chance, I would have gone in for research in molecular biology, specifically into epigenetics. I love to read mostly about molecular biology, but also on quantum physics, and cosmology. I have an innately inquisitive nature. My first interests were nature and magic. I was always curious to know what lies behind the facts, and unravel the hidden processes of that which is not visible and not evident. It was one of the main reasons why I chose medicine.

TS: I KNOW THAT YOU FIND GREAT SOLACE AND PLEASURE IN A SPECIAL KIND OF GARDENING. CAN YOU AMPLIFY?

Indeed, and it all started thanks to my curiosity. I came across a book about bonsai trees and was instantly enthralled, because as I read, 'how can a tree which in the wild is so big and majestic, be grown on a much smaller scale in such a small pot, surely there are hidden secrets involved!' After reading this book, I was hooked for life. The Bonsai Culture Group-Malta already existed and I joined immediately. It was the best thing I could have done. Whoever becomes interested in bonsai generally makes a rudimentary mistake of doing it alone. This only results in catastrophes. A group will guide you about the bonsai's growth process, techniques, etc. Eventually, I became the Bonsai Culture Group's General Secretary and have been so for the past 16 years. The fact that I like to organise events and bring people together has helped me immensely.

TS: CAN YOU TELL ME SOMETHING MORE ABOUT BONSAI?

Well the culture was born in China but the Japanese took it to a much higher level, by establishing styles and strict rules. I personally prefer classical bonsai styles although there are now several schools of thought which prefer 'modern' style bonsai. Whichever the style, the basic horticultural techniques remain the same and must be fully mastered for success. Some bonsai trees can be grown from seed. Others grow from cuttings. Nonetheless, on average, a bonsai will take anything between five and eight years to reach an accepted level of maturity from such humble beginnings.

Also one needs to point out that bonsai is a living art form with four dimensions, where time is of utmost importance, since certain aspects need time to be achieved and also, no true bonsai is ever actually ready. Bonsai cultivation can serve as a de-stressor especially if you go into its philosophical connotations. Indeed, as a famous bonsai artist John Naka once said, 'Bonsai must have philosophy, botany, artistry and human quality behind it to be a bonsai' and 'The bonsai is not you working on the tree; you have to have the tree work on you.'

For more information about the art of making bonsai, please visit www.bonsaimalta.org/

At home, with some of my pets in my self-made wooden greenhouse on the roof.

I READ THE SYNAPSE BECAUSE...

There is always something that interests me and intrigues me to further it by doing some research. Also I like the editorial which is so nudging and suggestive and at times entertaining but always with subtle useful messages.

LETTERS TO THE EDITORS

DEAR EDITORS,

I would like to comment on the article '*A Case Report and Overview of Carbamate Insecticide (Baygon) Poisoning*' published in the last issue (Issue 6 of 2017), authored by Drs Peter Muscat and Marlene Attard.

In their First Aid Measures (first aid for inhalation) section, they write "If the person is not breathing one should call for an ambulance then start artificial respiration, preferably mouth-to-mouth, if possible."

I feel that this is unsafe advice. Poisons acting via the inhalational route can cause harm to the first-aider through mouth-to-mouth respiration. The first principle of first aid and resuscitation is safety, of the rescuer and the patient. Publications and recommendations regarding this topic include:

1. Truhlář A, Deakin CD, Soar J, et al. *European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances.* Resuscitation 2015;95:148-201. Available from: https://cprguidelines.eu/sites/573c777f5e61585a053d7ba5/content_entry573c77e35e61585a053d7baf/573c78115e61585a053d7bce/files/S0300-9572_15_00329-9_main.pdf? Page 18 of the article states the following: **"Modifications to resuscitation:**
   - **Have a low threshold to ensure your personal safety where there is a suspicious cause or unexpected cardiac arrest. This is especially so when there is more than one casualty.**
   - **Avoid mouth-to-mouth breathing in the presence of chemicals such as cyanide, hydrogen sulphide, corrosives and organophosphates."**
2. Koksal N, Buyukbese MA, Guven A, et al. *Organophosphate intoxication as a consequence of mouth-to-mouth breathing from an affected case.* Chest 2002;122(2):740-1.
3. Nashijima DK, Wiener SW, John T VanDeVoort, et al. *Organic phosphorous compound and carbamate toxicity treatment and management.* Medscape, 2016. Available from: https://emedicine.staging.medscape.com/article/816221-treatment#showall. Here the advice is to use personal protective equipment (PPE) and mechanical ventilation when indicated.
4. Aardema H, Meertens JH, Ligtenberg JJ, et al. *Organophosphorus pesticide poisoning: cases and developments.* Neth J Med 2008;66(4):149-53. The advice is again to use PPE and mechanical ventilation if needed.

I felt that the above should be brought to your attention, considering the wide readership and reliable reputation of The Synapse in providing CME.

Best regards and thank you for your time.

Dr Petramay Attard Cortis

Specialist - Anaesthesia and Intensive Care Medicine

DEAR EDITORS,

I would like to make some comments regarding the article *'A Case Report and Overview of Carbamate Insecticide (Baygon) Poisoning'* published in Issue 6 of 2017 authored by Drs Peter Muscat and Marlene Attard. The authors describe a case of a gentleman who "experienced excessive exposure to Baygon" which they describe as a "local carbamate insecticide spray". In fact the whole article is based on the assumption that Baygon is a carbamate spray. I suspect that this is a wrong assumption.

In reality Baygon is a popular trade name of a multitude of different formulations of various insecticides. The constituents of Baygon preparations differ in various countries. Baygon is marketed as a carbamate only in certain formulations of agricultural grade insecticides containing propoxur formulated as granules or powders in a few countries around the world (including USA). Aerosol and spray formulations especially those indicated for household use are invariably a combination of two or more pyrethroids such as imiprothrin, cypermethrin, prallethrin, d-phenothrin, cyfluthrin, tetramethrin, d-allethrin and transfluthrin. Many times these may be co-formulated with other ingredients such as piperonyl oxide which are added to prolong the activity of such pyrethroids. Baygon preparations marketed in Malta in fact contain either a combination of imiprothrin and cypermethrin or a combination of prallethrin and d-phenthrin; in any case always pyrethroids and not carbamates.

This difference is important since both the toxicity as well as the management of pyrethroid toxicity is markedly different from that of carbamate toxicity. In a nutshell pyrethroids do not inhibit acetylcholinesterase and thus there is NO role for atropine or for any oxime to be used in pyrethroid intoxications.

In their description of how to tackle carbamate toxicity the authors also recommend "artificial respiration preferably mouth-to-mouth". In reality when treating patients presenting with symptoms of pesticide contamination, it is crucial that first responders wear appropriate personal protective equipment. If the patient has not been decontaminated, secondary carers must also wear appropriate personal protective equipment for chemical exposure to avoid contaminating themselves.

In their mentioning of atropine treatment [indicated in the treatment of organophosphate and/or carbamate intoxications but NOT of pyrthetrins/pyrethroids] the authors mention a particular regimen. In fact many guidelines recommend other doses and regimens which are demonstrated to speed atropinisation and reduce mortality. One such regimen involves starting with a 2mg dose of atropine given intravenously, then doubling the dose every 5 to 10 minutes until clinical improvement is evident. However beyond that, the authors state that the dose of atropine given should maintain the patient fully atropinised, then mentioning dilated pupils as an endpoint of atropinisation. This is in fact a common fallacy in the

treatment of such intoxications. When a patient is exposed to an anticholinesterase [such as carbamates and organophosphates] the pupils will remain constricted for a number of days, thus pupil size should not be used as an endpoint for atropinisation.

The authors later on in the case report use an 18 year old paper to make a blanket recommendation to perform "gastric lavage ... in every unconscious poisoned patient". Such a recommendation is unwarranted and can be dangerous. First of all gastric lavage is to be contemplated only in an oral ingestion and not in an inhalational exposure as described by the authors. Your readers may refer to the latest Position Paper on Gastric Lavage as issued by the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists (Benson BE, Hoppu K, Troutman WG et al. *Position paper update: gastric lavage for gastrointestinal decontamination.* Clin Toxicol (Phila) 2013;51(3):140-6) which concludes that "at present there is no evidence showing that gastric lavage should be used routinely in the management of poisonings. Further, the evidence supporting gastric lavage as a beneficial treatment in special situations is weak, as is the evidence to exclude benefits in all cases. Gastric lavage should not be performed routinely, if at all, for the treatment of poisoned patients. In the rare instances in which gastric lavage is indicated, it should only be performed by individuals with proper training and expertise".

In the context of a carbamate or organophosphate oral intoxication one should consider gastric lavage with a nasogastric tube, only if a substantial amount has been ingested within an hour and where the practical expertise exists. In such cases great care should be taken to protect the airway particularly if consciousness is depressed or as in many cases, a hydrocarbon solvent is also implicated. In the context of a pyrethroid intoxication, gastric lavage is in fact not recommended, also because some formulations may contain solvents and gastric lavage may in turn significantly increase the risk of aspiration pneumonia and pneumonitis.

Your readers may also find it useful to note that the Malta Competition and Consumers Affairs Authority [MCCAA] maintains a database of registered biocidal products in Malta which is available at http://mccaa.org.mt/en/legislation-documents and a list of approved plant protection products which is available at http://mccaa.org.mt/en/placing-on-the-market.

Regards and wishing you all the best,

Mr Mark Zammit

General Secretary, European Association of Poison Centres and Clinical Toxicologists

Advanced Pharmacy Practitioner, Central Procurement and Supplies Unit, Ministry of Health, Malta

The editor board wants to clarify that the article was, indeed, peer reviewed. At this stage, the board has decided to completely remove the article from the online database.

EXPOSURE TO "HOME" INSECTICIDES

- Common insecticides (e.g. Baygon) indicated for household use are invariably a combination of two or more pyrethroids (e.g. imiprothin, cypermethrin, etc) together with other chemicals. They do not contain carbamates or organophosphates.
- The risk of pyrethroid toxicity is usually low.
- The use of permethrin as a topical treatment or shampoo for head lice or scabies is associated with relatively low risk of toxicity if used according to directions.
- Prolonged exposure to pyrethroids can cause a range of clinical features such as paraesthesia and respiratory irritation. Significant exposure, normally from large ingestions of the undiluted formulation [as mostly used in agriculture], can lead to more severe symptoms including respiratory failure, coma and convulsions. Patients with a history of large ingestions should usually be observed for at least 4-6 hours for any signs of CNS depression or seizures.
- There is no specific antidote to pyrethroid toxicity. Management is via conventional means and attention to life threats. There is no role for gastric lavage in pyrethroid toxicity. Gastric lavage has been associated with increased risk of aspiration and chemical pneumonitis in the unprotected airway.
- Minor cutaneous symptoms should be managed with copious soap and water. Creams containing Vitamin E have been anecdotally reported to relieve paraesthesia.

Mr Mark Zammit

General Secretary, European Association of Poison Centres and Clinical Toxicologists
Advanced Pharmacy Practitioner, Central Procurement and Supplies Unit, Ministry of Health, Malta

Dr Robert Chircop

Head of Emergency Medicine, Gozo General Hospital
Clinical Toxicologist

BIBLIOGRAPHY

1. Bradberry SM, Cage SA, Proudfoot AT, et al. Poisoning due to pyrethroids. Toxicol Rev 2005;24(2):93-106.
2. He F, Wang S, Liu L, et al. Clinical manifestations and diagnosis of acute pyrethroid poisoning. Arch Toxicol 1989;63: 54-8.
3. Giampreti A, Lampati L, Chidini G, et al. Recurrent tonic-clonic seizures and coma due to ingestion of type I pyrethroids in a 19-month old patient. Clin Toxicol 2013; 51:497-500.
4. Database of biocidal products in Malta - http://mccaa.org.mt/en/legislation-documents.
5. Khasigian P. Pyrethrins and Pyrethroids. In: Olson KR, et al. eds. Poisoning and Drug Overdose. 7th ed. New York: McGraw-Hill Education; 2017.
6. Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):140-6.
7. Holland MG. Insecticides: Organic Chlorines, Pyrethrins/Pyrethroids, and Insect Repellants. In: Hoffmann RS, et al. eds. Goldfrank's Toxicologic Emergencies. 10th ed. New York: McGraw-Hill Education; 2015.

Augmentin® ES

600 mg/42.9 mg/5 ml

Amoxicillin/Clavulanate Potassium

Powder for oral suspension

- ✓ Provides extended antibacterial coverage to include the most penicillin-resistant strains.[1]
- ✓ Recommended by leading Guidelines as first line treatment in AOM.[2,3]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.[4]
- ✓ Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

Spreading infectious energy!

Mini Abridged Prescribing Information: *Please refer to the full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAMES:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATIONS:** Supplied in 100 ml glass bottle with a dosing spoon. **INDICATIONS:** Treatment of acute otitis media and community acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY & ADMINISTRATION:** Oral use; recommended dose of 90/6.4 mg/kg/day in two divided doses. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Augmentin ES contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). *Refer to the SPC for full list of precautions.* **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥ 1/10): diarrhoea. Common (≥ 1/100, < 1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to the SPC for full list of undesirable effects.* **AUTHORISATION NUMBER:** AA 1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** May 2016 **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)** ***REPORTING ADVERSE EVENTS (AEs):*** **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131) **Alternatively, any suspected AEs and m edication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

References:

1. Anthony R. White *et al*. Augmentin® amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent Journal of Antimicrobial Chemotherapy (2004) 53, Suppl. S1, i3–i20.
2. Gilbert DN, *et al*. Sanford guide to Antimicrobial Therapy v.3.11 – last updated March 11, 2014. Sperryville; Antimicrobial Therapy, Inc. 2014.
3. Lieberthal AS *et al*. The Diagnosis and Management of Acute Otitis Media. Pediatrics. 2013; 131; e964 Epub 2013 Feb 25.
4. Augmentin ES Summary of Product Characteristics, May 2015.

Prepared: November 2016 Job No: MLT_GIB/AES/0001/15(3)

For more information and dosing instructions:
www.hcp.gsk.com.mt/products/list/augmentin.html