Maltese Family Doctor

It-Tabib tal-Familja

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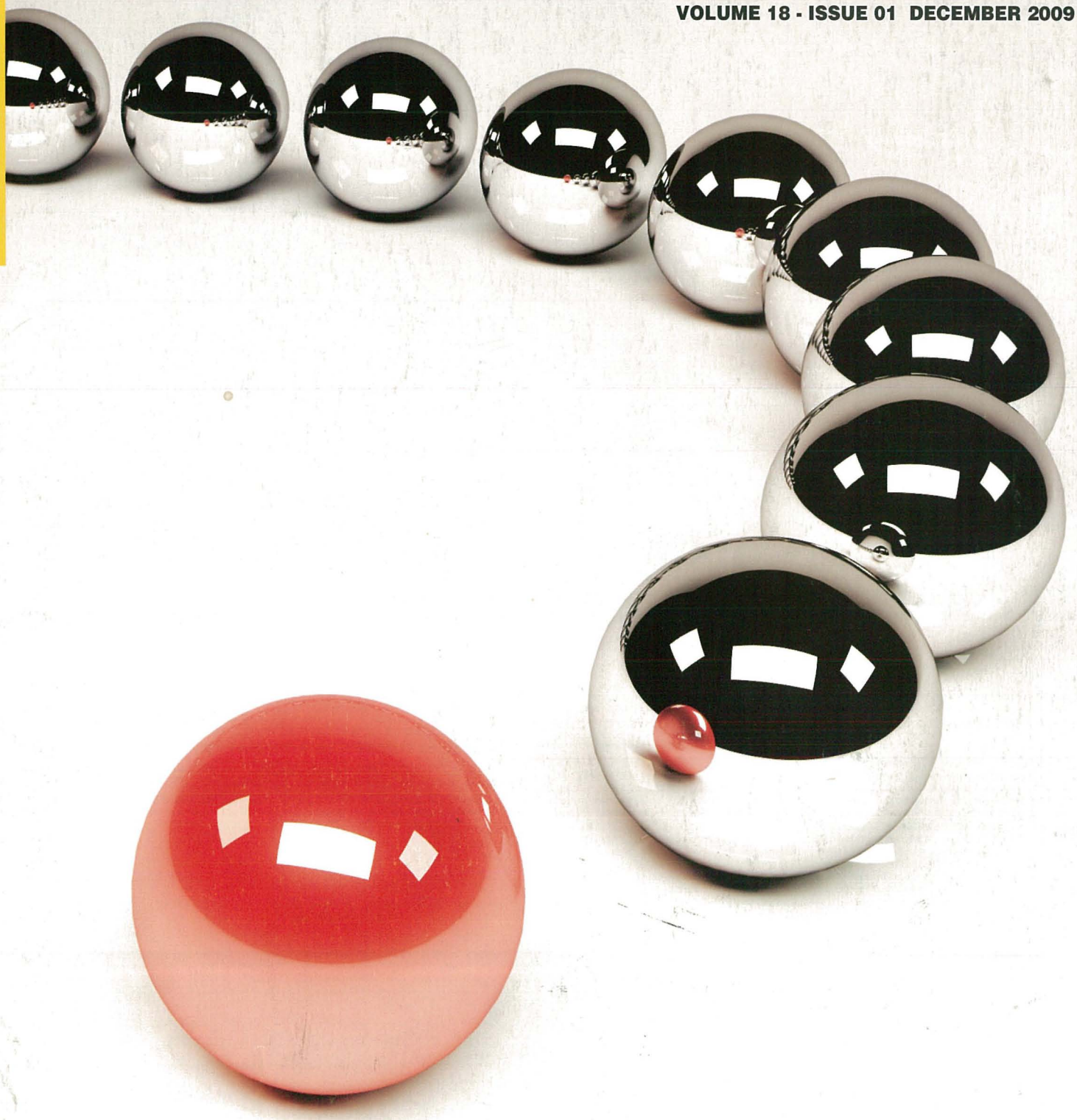

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The mission of the Maltese Family Doctor is to deliver accurate, relevant and inspiring research, continued medical education and debate in family medicine with the aim of encouraging improved patient care through academic development of the discipline. As the main official publication of the Malta College of Family Doctors, the Maltese Family Doctor strives to achieve its role to disseminate information on the objectives and activities of the College.

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Leadership with a small 'l'

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Leadership with a small 'l'

Dr Noel CARUANA

Towards the end of summer our membership was called to select a group of doctors who are to lead the college through new and tough, yet exciting challenges that lay ahead. Looking back at the past six years I served as college secretary I wonder what went well and what could have been done better. One thing that I feel we should have, are doctors with a sense of leadership, even if they would be leaders without grand visions, or leaders who are intrinsically introverts without fabulous oratory skills.

It appears that leadership insecurity is a common feeling, and many times when I urge colleagues to volunteer for leadership, the most common comment I get is, " I'm not a leader but…". Many times the "but" is something that reveals the individual is, in fact a leader. "But I want to change things in my practice", "but I want to change things to improve the health of…"

We need leaders in primary care who can combine personal humility and professional will, who understand cooperative leadership, they need to allow others to demonstrate their skills and strengths; know when to lead from the front and when to take a back seat and support and encourage their colleagues.

We have many hard working family doctors, who strive to improve their service and the health of the people they care for. The way we are practicing family medicine in our society may need to evolve and adapt to ongoing change.

On the eve of a new year, we are being told that we are on the eve of a reform in primary care. One hopes that whoever has the responsibility to pull this mammoth event through, has the wisdom to appreciate that the long term success of his policy lies in negotiation and not through unilateral imposition.

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A Service for Grown up Patients with Congenital Heart Disease (GUCH) in Malta

Prof Victor GRECH, Dr Oscar AQUILINA, Prof Jane SOMERVILLE

Introduction

Untreated congenital heart disease takes a heavy toll for those born with such anomalies, with approximately 65% dying in infancy and 15-20% reaching adolescence and adulthood.[1] Malta has had the same incidence of congenital heart disease in live births as other European countries, i.e. 0.8/1000 live births.[2] It has been fortunate to be able to give children optimal therapy by the ability to send infants and children to London for treatment including open heart surgery over the last 40 years. The majority have returned improved or cured, with diminishing mortality rates (figure 1) and increasing survival rates in the region of 95%.[3] Many have passed adolescence becoming parents and even grandparents, and are or have been in full employment, contributing to the community.

Potentially, once such patients leave childhood, their contact with paediatricians is lost and they often may have no regular medical supervision. Frequently, this is important, particularly for those with complex problems as well as those who have had valves replaced.

The importance of this new and ever expanding cohort of grown-up congenital heart (GUCH) patients is known but establishing optimal medical services for GUCH patients over the last 25 years in the UK has been difficult with the UK's established example followed with reluctance. In 1988, the European Society of Cardiology formed a special working group (number 22) to lead activities in Europe and assist policy making with guidelines.[4] Canada has formed a good network and has produced exemplary units lead by Toronto and the USA, despite two Bethesda reports lags behind.

Key Words

Heart defects, congenital

Grown-up congenital heart disease (GUCH)

Cardiology Service, Hospital

Cardiac Care Facilities/manpower/ *organization & administration

Mater Dei Hospital has established a clinic for adult congenital heart patients and those who need to change from paediatrics to adult cardiology care. This clinic was established by two of us (VG and OA) and has recently been joined by Professor Jane Somerville who pioneered the speciality and was responsible for establishing the services in UK and in Europe, as well as other parts of the world.

The outpatients clinic is held monthly, and is open to all patients with congenital heart disease aged 14 years and over, males and females, and also patients with Marfan, Turner, Noonan and other syndromes wherein heart and blood vessel pathologies are implicated.

The clinic is growing and there are now several hundred patients on the clinic database which has been maintained since 1994.[5] The intention of this article is to draw attention to this new service and encourage referral of all patients with congenital heart disease for assessment of their condition and any medical needs, such that Maltese GUCH patients can receive appropriate and optimal followup if required. The likely requirements of this service is reviewed by surgical survival rates for congenital heart disease for Maltese patients.

Methods

The Maltese Paediatric Cardiology Database was queried to obtain all patients operated for congenital heart disease. Cardiac conditions were subdivided into two:

Severe CHD included those lesions with all valves and chambers present. These lesions can usually be completely repaired with a biventricular circulation i.e. with one ventricle supporting the systemic circulation and another ventricle supporting the pulmonary circulation.

Complex CHD included those lesions with valve and/or chamber atresia and/or hypoplasia. Generally, complex lesions can only achieve extended palliation via extensive surgery with a univentricular circulation i.e. with one ventricle supporting the systemic circulation

and no ventricular support to the pulmonary circulation. Flow across the lungs is achieved by passive flow from the venae cavae.

Patients

All patients diagnosed as having CHD, who were born up to 2004 inclusive, and operated for CHD up to 2004 inclusive were included in this study.

Population

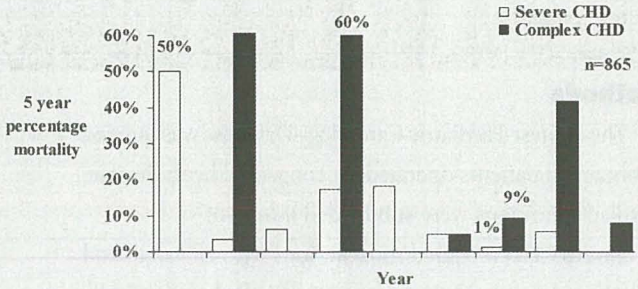
The catchment area for this study were the Maltese Islands. Mater Dei Hospital is the only regional hospital in Malta, and caters for the investigation of all patients suspected of having CHD, and their follow up.

Results

865 operations were documented for severe and complex lesions. The first operation for CHD on a Maltese patient was performed locally by a Maltese team and this was ligation of a patent ductus arteriosus in 1947. There was a five year hiatus after which patients began to be referred to The Hospital for Sick Children, London (GOSH) and to Guy's Hospital, London. Cases began to be referred to St. Mary's Hospital, London from 1966 up to the early 1980s. Referrals then began to be sent to Hammersmith and reverted primarily back to GOSH in 1988.

The percentage 5-year perioperative mortality decreased throughout the period under study overall, and for both severe and complex CHD.

Figure 1



5 yearly percentage early (1 month) percentage mortality for surgery for congenital heart disease in Malta. Complex lesions: univentricular hearts (e.g. tricuspid and pulmonary atresia). Severe lesions: biventricular hearts (e.g. ventricular septal defect closures, tetralogy of Fallot and coarctation repairs and arterial switch procedures for transposition of the great arteries). Extended from Grech V and Elliott MJ 1998.3xx

Discussion

Characteristics of the population

This is a young population with cardiac problems and has replaced rheumatic heart disease that was so prevalent 30-50 years ago. The needs of GUCH patients are different from the commoner type of adult cardiac patient with hypertension and coronary artery disease. They are younger, have many medical problems in systems other than the cardiovascular, as well as more social adaptive problems which require advice and support. These patients include the more complex conditions i.e. tetralogy, coarctation, atrioventricular septal defect, transposition of the great arteries, total anomalous pulmonary venous drainage, truncus arteriosus and univentricular hearts and does not include relatively simple and straightforward lesions such as pulmonary stenosis and ventricular septal defect.

A liaison nurse specialist is vital in this service so that patients can make direct contact for medical advice and appropriate referral. General services, all available at Mater Dei Hospital, are required by 20-25%, particularly obstetric services. The supervision of pregnancy and delivery and assessment of offspring and siblings requires the support of both cardiologist and obstetrician experienced in the care of those at cardiac risk in pregnancy.[6]

The GUCH patient population is slowly ageing. In the longer established units, 30% are over 40 years old and have lesions with present the health service with the usual spectrum of comorbidities. The main problems affecting GUCH patients are:

Cardiac problems

1. Arrhythmias (commonest)
2. Increasing cyanosis
3. Heart failure
4. Endocarditis
5. Emboli
6. Deteriorating symptomatic state
7. Need for reinvestigation

Facilities needed for the followup of GUCH patients include:

1. Usual cardiac tests e.g. ECG, CXR, exercise testing
2. Echocardiography by expert staff including transoesophageal echocardiography. Equipment must be modern with facilities to measure flow, volume and Doppler for both flow and tissues.
3. Electrophysiology
4. Pacing
5. Cardiac catheterisation

6. Sophisticated imaging techniques such as magnetic resonance imaging requires someone familiar with congenital heart disease and appropriate software.

Malta has most of these, but the services must be brought together for the sake of our GUCH population who must, in turn, be encouraged to attend specialist GUCH clinics. It is certain from the number of survivors from our database review that a significant number of our GUCH population is lost to followup. A recent local attempt to study all patients beyond infancy who had had tetralogy of Fallot repair only succeeded in tracing 57 patients out of a total of 100, with 43 therefore lost to followup.[6] This is in keeping with studies in larger countries which have clearly demonstrated that these patients exist and attend non-specialist clinics despite some of them having very complex heart disease.[7]

The plight and problems of GUCH patients have been recently highlighted locally in a conference at the Mediterranean Conference Centre in December 2008 (Mediterranean GUCH course), wherein an authoritative faculty discussed various aspects of this select population (www.maltime.com under past events).

A simple calculation based on published epidemiological data for the Maltese Islands, and assuming 95% survival shows that our pool of GUCH patients will incrementally increase by 12 patients per year, every year.

With the clinic now established, it is important to consolidate the service and make it efficient, embracing all the Maltese GUCHs. Patients with GUCH should therefore be referred to the GUCH clinic at Mater Dei Hospital for specialist assessment and followup.

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Secondary Metabolites and their Exploitation in Medicine

Dr Alfred GRECH, Dr Alexandra BALDACCHINO and Dr Marcel TUFIGNIO

Many of the medicinal products available today are derived from secondary metabolites. Plants remain the main source of such therapeutic agents but other sources are being explored and exploited. New and old technologies are being applied in the continuing quest of finding useful secondary metabolites of plant origin or otherwise from which newer drugs can be made.

Introduction

Secondary metabolites are organic compounds that are not directly involved in the normal growth, development or reproduction of organisms (Petr Karlovsky, 2008). It is in this sense they are called "secondary" but this does not imply that they are in anyway unimportant. They exert various biological effects, often at very low concentrations, and can be regarded as carriers of chemical communication among organisms.

Contrary to primary metabolites, secondary metabolites are not ubiquitous in the living organisms which produce them and they are rarely conserved over a wide taxonomical range (c.f. primary metabolism is conserved among phyla and across kingdoms). Usually, they are produced through a long chain of intermediates involving several enzymes. Generally they are created from modified primary metabolites, or from substrates of primary metabolite origin. Some are produced all the time (i.e. constitutively) while others are produced after induction.

By now, some 150,000 natural products are known, of which about 80% originate from plants.

Functions of Secondary Metabolites to the Organism

The function of secondary metabolites is usually of an ecological nature. Some are used by the organism to defend itself against its predators, parasites and diseases. Others are used for interspecies competition, or to facilitate the reproductive processes e.g the coloring agents and the attractive smells of flowers are usually secondary metabolites. They may also function in such other processes as immunity, anti-herbivory, maintaining symbiotic associations or communication between organisms (e.g. VOCs = volatile organic compounds; bacterial autoinducers).

Bacterial cells use secondary metabolites to chemically communicate with each other in a process called quorum sensing (QS). Quorum sensing in bacteria is the regulation of gene expression as a function of the cell-population density. The bacteria produce and release chemical signal molecules called autoinducers. Usually as the bacterial population density increases, the concentration of the signal molecules increases as well. When the bacterial population reaches a critical level called the quorum, the bacteria respond and modulate certain gene expression (like genes coding for virulence) almost simultaneously.

Gram-positive and Gram-negative bacteria use quorum sensing to regulate a diverse array of physiological activities such as symbiosis, competence, conjugation, antibiotic production, motility, sporulation, virulence and biofilm formation. In general, Gram-negative bacteria use acylated homoserine lactones (AHLs) as autoinducers, and Gram-positive bacteria use processed oligo-peptides to communicate. This cell-to-cell communication via autoinducers occurs both within and between bacterial species. Indeed, furanosyl borate diester has been found to be employed by certain bacteria for interspecies communication (Chen et al. 2002).

Research is showing that with quorum sensing, the bacteria are becoming 'multicellular'. And doctors should no longer think that bacteria are asocial, single cells. They are individual cells but they act in communities. Researchers in various labs all over the world are now trying to find out exactly how bacteria chemically 'talk' to each other. Hopefully, they will know how to control and manipulate

Table 1

Medical Use	Medicinal agent	Source
Anti-tumour	Vincristine, VinblastineTaxol, Ursolic acid Discodermolide	Catharanthus roseus, Taxus sp., Lichens Discodermia dissoluta
Antibiotic	Abyssomicin, Vancomycin, Streptomycin Bacitracin, Penicillin, Erythromycin, Usnic acid	Actinobacteria, Bacillus subtilis Penicillium, Saccharopolyspora erythraea, Lichens
Antiviral	Depsides, Depsidones Virsenic acid, Stictic acid Chlorophaeic acid, Podophyllin	Lichens Podophyllium
Antimalarial	Quinine	Cinchona ledgeriana
Cardiotonic	Digoxin	Digitalis lanata
Antihypertensive	Reserpine, Ajmalicine	Rauwolfia serpentina, Catharanthus roseus
Analgesic	Morphine	Papaver somniferum
Anti-pyretic Anti-inflammatory	Salicylic acid	Salix
Anti-cholinergic	Atropine, Hyoscyamine, Scopolamine	Atropa belladonna, Hyoscyamus niger Datura metel
Cholinergic	Pilocarpine	Pilocarpus sp.
Anti-gout	Cochicine	Colchicum autumnale
Antifertility	Steroids from Diosgenin	Dioscorea deltoidea
Anti-tussive, Antidiarrheal	Codeine	Papaver somniferum

quorum sensing and tailor make anti-quorum sensing drugs. One line of research is the demonstration that certain plants and red algae are able to mimic QS signals produced by several bacteria by secreting compounds that structurally mimic the bacterial QS molecules (Newton and Fray 2004; Bauer and Mathesius 2004). Specifically, the marine red alga Delisea pulchra produces halogenated furanones which act as QS 'mimic' compounds. These halogenated furanones have a similar structure to AHLs. Interestingly, such furanones inhibit AHL-regulated behaviours in several bacteria (Teplitski et al. 2000).

Medical Uses of Exploited Secondary Metabolites

The following valid and instructive example shows the potential of exploiting secondary metabolites for medical use. Doctors are worried that unless scientists find novel antibiotics within a short time, they would find themselves back in the era of life-threatening bacterial infections. A case in point is the superbug, MRSA, which is now resistant to most antibiotics. By exploiting marine microbes (specifically, a group of bacteria called Actinobacteria), researchers have come across a new class of antibiotics. Usually, such bacteria came from soils and researchers believed that there were no marine species of Actinobacteria. But Actinobacteria are also found in seawater sediments, from continental shelves to the abyssal depths. Indeed, a marine sediment may contain more than 1000 new species. Scientists have found a bacterium from such a sediment at a depth of 300 metres in a bay in Japan. This bacterium produces a secondary metabolite that acts as an antibiotic to control the growth of other micro-organisms in its niche. This antibiotic has been rightly named **abyssomicin**. Investigations and tests on abyssomicin are showing promising results in that it kills MRSA. Also, by studying the mode of action of abyssomicin it has been found that it disrupts pABA synthesis. Therefore, this may also make abyssomicin a potential anti-malarial drug.

Some of the medical uses of some secondary metabolites are shown in Table 1 above.

Some Specific Examples of Exploitation of Secondary Metabolites

From Plants

Plants have been used in the treatment of cancer for over 3500 years (Hartwell,1967). This is evidenced in the

folklore of many countries. For example the Chinese used podophyllum leaves and many other countries used the juice of Bittersweet (Solanum dulcamara) to treat cancers, tumors and warts. But it is only since 1959 that a systematic effort has been made to screen crude plant extracts for their inhibitory activity against tumour systems.

The number of medicines used in chemotherapy is around 20. These comprise synthetic and natural drugs (Lee, 1999). Most of the active principles act upon DNA by modifying its chemical and physical nature. On the basis of mechanisms of action the antitumour agents can be broadly categorized in 4 groups: (1) alkylating agents, (2) antimetabolites, (3) mitotic inhibitors (spindle fibre toxins) and (4) intercalating agents. Caryolysine was among the first alkylating antitumoral agent in the class of nitrogen mustard used for the treatment of human cancers. Chlorambucil, melphalan and mannomustine are other alkylating products that were developed later. Fluorouracil and methorexate are examples of antimetabolites, while colchicine, taxol and vinblastine (a vinca alkaloid) are mitotic inhibitors. Quinine, quinacrine, ellipticine, ethidium bromide, nitidine and actinomycin-D are all examples of DNA intercalating agents. Of these taxol is the latest and is obtained from the bark of yew, Taxus. Taxol is used for the treatment of breast, ovarian, lung, bladder, prostrate, melanoma, esophageal, as well as other types of solid cancers.

Other medically exploited secondary metabolites derived from plants include atropine, codeine, morphine, and digoxin. Atropine is extracted from deadly nightshade (Atropa belladonna), jimsonweed (Datura stramonium), mandrake (Mandragora officinarum) and other plants of the family Solanaceae. Morphine is the principal active agent in opium and other poppy saps like Papaver bracteatum. It was the first alkaloid isolated from a plant source, and was named morphium after Morpheus, the Greek god of dreams. Codeine (methylmorphine) is also found in opium and while it can be extracted from opium, most codeine is synthesized from morphine through the process of O-methylation. Digoxin (Digitalis) is a cardiac glycoside extracted from the foxglove plant, Digitalis lanata.

From Bacteria

Vancomycin is a glycopeptide antibiotic derived from the Actinobacteria species Amycolatopsis orientalis. It was first isolated from a soil sample collected from the interior jungles of Borneo by a missionary.

Streptomycin is another antibiotic, the first of a class of drugs called aminoglycosides to be discovered. It was the first antibiotic remedy for tuberculosis. It is derived from the actinobacterium Streptomyces griseus. **Neomycin** is also an aminoglycoside antibiotic that is found in many topical medications such as creams, ointments and eyedrops. It is produced naturally by the bacterium Streptomyces fradiae.

Another topical antibiotic is **Bacitracin.** It is produced by Bacillus subtilis.

From Fungi

Fungi also offer a huge source of pharmaceutically useful molecules. For the fungi the discovery of penicillin marked a new era. Penicillin is an antibiotic that is derived from the fungus Penicillium. Another useful antibiotic is erythromycin. It is produced from a strain of the actinomycete Saccharopolyspora erythraea found in soil.

The genus Claviceps is a fungus that is parasitic on certain grains and grasses. In winter the fungus forms a sclerotium usually referred to as an 'ergot'. These ergots are hard, black tuber-like bodies which consist of a compact mass of hyphae. Such ergots produce up to 40 different alkaloids. The main ergot alkaloids are ergotamine, ergocornine, ergocristine, ergocryptine, ergometrine and agroclavine. If ergot alkaloid-containing grasses and cereals are eaten, ergotism results ("St. Anthony's Fire").

Some of the ergot alkaloids have been medically exploited. Historically, controlled doses of ergot were used to induce abortions and to stop maternal bleeding after childbirth. Nowadays, one also finds nasal drops containing ergometrin (Methergin) to stop postnatal bleeding; Cafergot (containing caffeine and ergotamine or ergoline) to treat migraine headaches. Another two important ergot-derived drugs are Pergolide and Cabergoline. Pergolide (Permax) is a dopamine receptor agonist and is used for the treatment of Parkinson's disease. Pergolide products were removed from the market in 2007 because of the risk of serious damage to patients' heart valves. Nowadays, if indicated the patient should be regularly reassessed for any fibrotic reactions and valvulopathy. Cabergoline (Dostinex) is also a dopamine receptor agonist. It is indicated for the treatment of hyperprolactinemic disorders.

From Lichens

Lichens are associations between a fungus (the mycobiont) and a primitive photosynthetic organism (the photobiont). The latter is either a green alga or a

cyanobacteria. Approximately 700 secondary metabolites have been identified in lichens. Many of these compounds are the result of the symbiosis. Indeed, the majority of the organic compounds formed in lichens are secondary metabolites produced by the fungal partner (Huneck and Yoshimura, 1996).

Lichens have a long history of usage in herbal medicines. Even though their therapeutic potential has not been yet fully explored, the following biological activities of some lichen secondary metabolites have been investigated and exploited.

Usnic acid has antibiotic activity. Compositions containing usnic acid or its derivatives are used for therapeutic control of dental caries, particularly for the preventive treatment of cariogenic dental plaque. Usnic acid is bacteriostatic against the gram-positive Streptococcus mutans which is the primary pathogen in cariogenic lesions. Many tooth pastes and mouthwashes used for dental and oral cavity medications contain usnic acid.

Ursolic acid has anti-cancer activity. The use of ursolic acid for the manufacture of an anticancer agent that suppresses metastasis has been patented (Ishikawa et al, 1997). Other lichen secondary metabolites that exhibit antitumoral effects include: **nephrosternic acid**, **polyporic acid** and its derivatives and **evernic acid**.

Depsides and **depsidones** have antiviral-activity against HIV virus. They inhibit HIV-integrase and are being investigated as potential AIDS treatment. **Virsenic acid**, **stictic acid** and **chlorophaeic acid** also show important effects against HIV-1 integrase. (Neamati et al., 1996).

The screening of crude extracts of numerous species of the lichen family Graphidaceae have demonstrated inhibition of the enzyme tyrosinase. **Tyrosinase inhibitors** have become important as cosmetic and medicinal products, primarily to control melanin pigmentation.

It has been shown that some secondary metabolites from lichens (e.g. **divaricatic acid**, **atranorin**) protect against oxidative damage by inhibiting the formation of free radicals and/or trapping reactive oxygen species. (Marante et al., 2003).

Other lichen products have analgesic, anti-inflammatory, or anti-pyretic activities. For example **chrysophanol** has been shown to be a potent anti-proliferative and anti-inflammatory agent in the treatment of psoriasis (Muller, 2001).

Pannarin and **chloropannarin** have been shown to have antiprotozoal activity.

From a Sponge

Discodermolide is a recently discovered polyketide natural product found to be a potent inhibitor of tumor cell growth by hyper-stabilizing microtubules. It was first isolated in 1990 from the Caribbean **marine sponge** Discodermia dissoluta. Discodermolide also has immunosuppressive and antifungal activities. Several preclinical drug development programs are ongoing.

Current Research on Secondary Metabolites

Production of Secondary Metabolites by Bioconversion and Precursor Feeding

Plant cells are omnipotential, meaning that all the genetic information present in the plant is principally available in each cell. Hence theoretically, genes that encode enzymes of biosynthetic pathways can be brought to express themselves. It is thus feasible to produce most plant secondary metabolites using in vitro grown cultures. The successful production of antibiotics by fungi and bacteria was the stimulus for the initial plant biotechnologists to have a try with in vitro plant cell cultures. But it soon became clear that plant cell cultures do not always accumulate either qualitatively or quantitatively the same compounds found in the parent plant from which they were established. Because of this only a very limited number of secondary metabolites can be produced commercially by plant cells on a larger scale in bioreactors. High production rates are only feasible for compounds with a simple chemical structure, such as L-DOPA (an important anti-Parkinson drug).

Unfortunately, pharmacologically active compounds have a more complex chemical structure e.g. podophyllotoxin and camptothecine which exert strong cytotoxic properties. Artemisin, a very potent new antimalarial drug and also the new cytostatic agent paclitaxel, have been produced in low amounts by Taxus cell cultures, progress is slowly being made and **precursor feeding** and **bioconversion** are very promising.

If the concentration of a compound which is an intermediate in a biosynthetic pathway is increased, this may increase the yield of the final product of the pathway. This is the basis of the precursor feeding approach.

Bioconversion is the modification of added precursors (also called substrates) into more valuable products using

enzyme catalysis. The systems used for bioconversion are (i) freely suspended plant cells (ii) immobilized plant cells and (iii) enzyme preparations.

Freely suspended cells are the most simple bioconversion systems, since precursors can be supplied directly to the cultures. The cell wall and cell membrane are the only barriers a precursor meets. The best way is to use plant cells that can do a one-step bioconversion but unfortunately the precursor often undergoes more than one bioconversion, resulting in complex mixtures of products. It can also be metabolized via unknown mechanisms. Nevertheless, a number of one-step bioconversions by freely suspended cells have been done. For example papaverine has been bioconverted using free cell suspensions of Glycyrrhiza glabra.

An **immobilized plant cells system** entails either entrapment of cells or immobilisation of cells. Immobilisation of the plant cells can be done by adsorption onto a support material. Entrapment methods include gel entrapment by ionic network formation and entrapment in performed structures (Novais, 1988). The most widely used approach is entrapment by ionic network formation, especially in the form of alginate beads.

Some successfully applied one-step bioconversions by immobilized cells have been done. For example the bioconversion of the precursor codenione into codeine using Papaver somniferum or the bioconversion of L-tyrosine into L-DOPA using Mucuna pruriens. Immobilized cells derived from various lichens have also been employed to produce useful secondary metabolites (Vincente et al., 2003).

Enzymes from plant cells are also being used to convert foreign precursors, intermediates that are not normally biosynthesized in the plants from which the cultures are derived (Kutney, 1996: Suga and Hirata, 1990).

Bioconversions and precursor feeding are yielding new drugs but they are also being applied for the improvement of currently used drugs. Hydroxylations and gylcosylations or a combination of both are most suitable for this purpose.

Recombinant DNA technology

Plant cells often make low quantities of the desired enzyme, resulting in low bioconversion rates. A solution may be found in the transfer of plant genes, which encode the enzyme into a bacterial (e.g. E.coli) or fungal cell (yeast) and more, recently, into insect cells. The idea is to bring the gene to overexpression in a preferably rapidly growing host cell, resulting in a high production of the desired enzyme (Overbeck and Verrips, 1992). This expression of genes encoding plant enzymes in a foreign host cell is termed **heterologous expression**: a gene is transferred from one cell species, a plant cell, to another cell species, the host cell (fungal or insect cell). This heterologous expression is also being tried (with some success) for the production of certain lichen metabolites. Recombinant DNA technology has not yet reached the stage at which large numbers of foreign genes can be transferred to any host cell and then coordinately expressed. This implies that the problems regarding the expression of more complex pathways (which usually have many enzymes) under in-vitro circumstances are not likely to be solved in the near future.

With all the above problems, still, the culture of plant cells or otherwise is feasible and can be used to produce significant amounts of secondary metabolites. For the development of an industrial process, the crucial question is its economic feasibility. At the time it is only for a small number of high-value compounds that this is economically feasible. However, research and many experiments are being done to improve productivity of other secondary metabolites from stable, high-yielding cell lines. The production of secondary metabolites on an industrial scale using bioreactor system designs is important because indiscriminate removal of plants or otherwise from the wild to meet the high demand of medicine for the ever-increasing human population, is making such wild sources endangered. A case in point is the exploitation of the Taxus tree for taxol. Taxus is a small tree that grows very slowly. Taxol is derived from its bark and its extraction leads to death of the tree. It is estimated that about 50kg of taxol will be required every year for the treatment of approximately 12,500 women in the USA alone. The present world demand may touch 250kg per year. Generally 30kg of taxol are obtained from 42,000 trees. So with some calculations this means that at least three Taxus plants are needed for one patient. Such a large number of plants are not available from the wild population.

Metabolomics

The set of metabolites synthesized by an organism constitute its **metabolome**. **Metabolomics** is the quantitative and qualitative study of all the metabolites present in a cell. By comparing the **metabolic profile** of a cell producing metabolites in high quantity to a similar cell that is not producing these metabolites, differences in gene expression is being recorded. Such studies form part of **functional**

genomics and it is helping in the identification of genes which are involved in product formation. It is also elucidating key steps and bottlenecks of metabolite synthesis. Metabolic profiling of the wild type, mutant and transgenic organism, is providing useful data in **metabolic fingerprinting**. Indeed, it is becoming possible to link metabolic changes in biochemical pathways to the enzymes involved, and then to the underlying genetic alterations.

Such metabolic studies are yielding huge data sets that need to be analyzed and stored. With replications and various samples taken during experiments, the number increases considerably, generating several hundred megabytes of data per experiment (Petr Karlovsky, 2007). The raw data obtained is then processed and converted to useful biological information by a variety of data analysis techniques. Evolutionary computation-based methods such as genetic algorithms and genetic programming are being found to be ideal strategies for mining such high-dimensional data to generate useful relationships, rules and predictions (Goodcare, 2005) and thus aiding the exploitation of secondary metabolites for medical use.

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The Pageant of Life and other Facets

Dr Charles J BOFFA

The story of human life dates back from written history through oral tradition to the records of geological, palaeontological and archaeological discoveries.

About 22 thousand years ago or earlier, Europe was held in thrall by probing masses of thick ice from the North of Europe to cover most of Great Britain, Northern Germany, Poland, Scandinavia, Switzerland and Russia, etc. Smaller ice-caps crept southwards covering Austria, Northern France and Northern Italy. Stone Age hunters struggled to survive hunting herds of reindeer, mammoth and other animals.

Great floods are mentioned in the Bible. Perhaps about 15,000 years ago, or so, the ice sheets began to retreat. Within about 10,000 years ago or so, these had withdrawn roughly from most of Europe.

I think that the less vigorous climate could have attracted a lot of migration south to the Mediterranean. I believe that the Mediterranean region owed its flowering and civilization, at least partially to its mild sunny climate.

Various valleys in Malta and Gozo, such as Wied iz-Zurrieq, Wied Babu, Wied Incita, Wied il-Kbir, Xlendi etc. are suggestive of large volumes of water passing through for long periods in ancient times.

Life is not a station. The nature and timing of the Pleistocene periods is not clear. The movements of early people in Southern Europe and in the central Mediterranean Islands were affected by various factors such as the availability of food, the ups and downs of temperatures, floods and changes in sea levels. A few silos previously on land at Pretty Bay, Birzebbuga are now underwater- a clear proof of the changes in sea level. It is likely that Malta was at least slightly larger in ancient times. The timescales are not easy to define.

We came into the picture as a Neolithic people, but we cannot exclude the possibility that there were some earlier settlers as suggested by Drs. Anton and Simon Mifsud in their very good book- Dossier Malta, Evidence for the Magdalenian (1997).

The old general division of the early inhabitants of Europe into Mediterranean, Alpine and Nordics only remain fairly useful to some extent, because over a very long period of centuries there have been extensive migrations from country to country, which have resulted in a wide population mix.

By and large, the Mediterranean race if it can be called so, was long headed with generally oval faced or almost so, and not tall. This type was fairly common around the Middle Sea. This description applies also to many of the Neolithic folk at Palestine, Annau and Lebanon.

It is surmised that the Neolithic civilization had started in central Asia, although as yet this has not been fully defined. Although one cannot be sure, it is sometimes said that the old long headed Caspian folk could have developed into the so-called Tardenoisean and learning something or more of the new civilization became gradually Neolithicised. These could have in due course formed part of the Neolithic stock of western civilization. Possibly (?) it is better to refer to a certain race group (Neoanthropic Man) who would have arrived in Europe in late Palaeolithic times and over millennia underwent slight modifications in stature and complexion. If this be so, the people of Annau and of the western Mediterranean, would be so to speak cousins and physically not very dissimilar. However, it seems to me that there is an element of conjecture regarding this theory.

The Maltese islands occupy a central position in the Mediterranean. This location made our Islands an important place for the various civilizations throughout the ages and this fact found expression in our people. In the blood of our people there is a mixture of Semitic. Sicilian, Italian, Greek, Arab, Spanish, French and to a limited extent also British and Nordic genes. There are also a few families of Indian origin.

Analysis of the ascent and settlement of the early settlers was and is still to some extent hampered by chronological uncertainty. Timescales are not easy to define and notwithstanding the advances made it is not easy to be precise.

Now Europe has a diversity of peoples. To some extent this applies also to Malta. In late September 2008, an interesting exhibition of 50 very good large portraits by Norbert Attard was mounted at Freedom Square in Valletta. This exhibition attracted a lot of attention and in my view raised awareness of the different facial physiognomies – characteristics of the present Maltese population and the diversity which is quite revealing. The genetic set-up must have been influenced considerably during the Greek, Roman and Arab occupations. There is a risk of suggesting too much completeness in the state of our knowledge of the past and there are gaps in our knowledge. There is no doubt that the

Phoenicians influenced the genetic mix in our Islands a lot.

A brief mention of the Etruscans is also opportune. These enterprising people dominated the central Mediterranean area from the 8th to the 14th centuries B.C. and had formed a league of the 14 city states in what is now Tuscany, Italy. The Etruscan fortunes were based partly on trade and piracy and started to decline after 500 B.C. when the Romans too who had lived under Etruscan rule for a century began to absorb their former masters into their own expanding empire.

A few Etruscan ships occasionally visited central Mediterranean islands which included the Maltese Islands and Pantelleria to shelter from storms and to collect water and food. A few old surnames in Tuscany also exist in Malta. Inheritance is not all about genetics, but genetics is linked with inheritance. Genetics includes a set of inherited features which are passed on from generation to the next.

There are various studies which purport to show that generally, behaviour is under genetic control. Most of inherited characteristics are more complicated than a single change in the DNA involves and environment and to some extent nutrition also play their part. Genetics includes a set of inherited instructions passed on from one generation to the next. Human attributes are coded on to the unique inheritance which everyone receives from ancestors. So heredity may be defined as the inborn capacity of the constitution of the cell or cells that form the starting point of the individual. Certain genetic traits are bound to present ambiguities. To give an example why is it that in Cyprus quite a number of children, above the average number of other Mediterranean islands, suffer from a certain type of inherited anaemia (W.H.O)

The human brain has been the subject of study even during the times of Aristotle. Yet even with the latest developments in laser technology and the wonder of microchips, the brain remains an enigmatic study, some of its functions still a mystery.

Gradually over the ages, the mind developed into a confident, growing alive entity with an expanding potential. One of the most crucial steps was that Man could organise and solve problems. Brain building went on and still gradually goes on.

Words are the means by which Man expresses his thoughts. With precision of language or languages, thoughts gained clarity as well as ease of expression. Brain power slowly but surely improves. In my opinion in broad terms, this is still going on in mankind.

The expansion of consciousness is indeed of great significance and has played a vital part in human greatness. This development is in my view one of the attributes, Almighty God gave to Man in his wisdom. It is a great gift that has made Man unique. Who would challenge the heightening of mental faculties. New inventions in different spheres show the stimulus in capabilities and mental potential which are part of the hallmark of Man's mind.

In countries bordering the Mediterranean littoral, there have been over the millennia, many migrations, trade contacts and repeated harrowing epidemics. As a result people in this area had experienced a lot of selection for resistance to certain diseases, imported from other countries and continents and causing a very large number of deaths before burning themselves out. The build-up of resistance to various diseases in European descendents was not just a result of elimination of those lacking resistance, but it was also supported by the genetic variety provided by extensive inter-population gene flow. Furthermore when these same diseases were brought, on occasions, to smaller more isolated and inbred populations, these same diseases hit once such as plague and found hosts that were minimally resistant.

There is evidence that for a period which could have lasted a few hundreds of years, perhaps around 2500 B.C., or so, judging from signs at the Hal Tarxien temples our islands could have been the victim of invaders, some epidemic or pestilence and lost all or most of their inhabitants and afterwards a Bronze Age people arrived. The change is a significant one; however the chronology is not fully clear.

Man is a unique creature. He has sensitivity, he has understanding, and he has imagination. He can do what no other creature has done before him; control his environment to some extent and adapt himself to it.

A nerve network evolves into a nerve system, with its hub a ganglion that is to some extent comparable to a telephone exchange or a computer. Eye, hand and brain have given Man unlimited power, capabilities and ingenuity. How all these started or developed is not easy to imagine – I believe that all these faculties came about through the intervention of a Supreme Being – God the Almighty.

It is time to refer briefly to the Mind and Molecules. Man is very adaptable. During a human lifetime, every molecule of our body is replaced many times over. Cells die and are replaced, the connections between them are made and broken thousands of times, perhaps despite the ceaseless ebb and flow of their molecular components.

Careful examination of skeletal remains and teeth can provide direct evidence about peoples, their anatomical characteristics, age at their death, physical features and injuries, certain characteristics and diet.

The development and eruption of human teeth have long been known to give an indication of age. At birth all the deciduous teeth are present on their crypts and the mandible describes almost a straight line from the condoyle to the symphysis. Between the seventh and tenth month

after birth the incisors push their way through their crypts and begin to erupt, the growth of their roots forcing them occlusally. By the end of the first year all the incisors have usually erupted and the molars and cuspids (deciduous) are undergoing rapid development. By this time the mandible has lost its straight line appearance and the angle has become more apparent.

The times of eruption of permanent teeth follow a pattern but can vary somewhat slightly in some people. This applies also within limits to the sizes of teeth.

Human beings enter adolescence at about twelve. Physiological adulthood occurs at about eighteen with the completion of fusion of most parts of the skeleton..

The emergence of the first permanent molar at 6 years marks the end of infancy, the emergence of the second permanent molar marks the beginning of adolescence, while that of the third molar or wisdom tooth the beginning (or a little later) the beginning of adulthood. The partial or full eruption of the wisdom teeth can besides other factors serve as good landmark during age assessing.

The nature of archaeological evidence provides much light on the ancient past. For topographical and chronological research, these finds are vital.

Dr. Joseph Baldacchino (Curator of Museums 1947-55) had noted that an ancient cave at Burmeghez near Mqabba had yielded many bones from about 70 skeletons and about 2250 teeth, but according to this erudite scholar only a small proportion of the teeth showed carious lesions and many showed attrition, irregularities, including fused roots. Teeth recovered from several Zebbug and other tombs also showed little dental caries but levels of attrition.

In the mid 1959's while foundations were being constructed for buildings at Ghajn Dwieli, Paola between Triq Isqof Buhagiar and St. Anthony Church a few ancient tombs were encountered. The find included some human bones and Copper age pottery. Dr H. Micallef and I were asked to measure two skulls, both of which were almost dolichocephalic.

In the early eighties while rubble and stony soil was being removed not far from ta' l-Erwieh, Tarxien (playground area) some small scattered fragmented pieces of human and animal bones, teeth and crushed pottery came to light. Bulldozers had been used during the trenching works while development of the playground was going on. It is a pity that a process of squeezing some information out of the fragmented bits and pieces was to the best of my knowledge never attempted, perhaps because this could not be done.

In May 1958, Prof. R. Butler who at that time taught anatomy at the University of Khartoum, Sudan, visited Malta and gave two lectures at St. Luke's Hospital. He had also been shown some skeletons and bones unearthed in Malta and asked for his opinion.

Among other things, he expressed the view that the ones he had been shown showed that most probably they were not from tall persons or from those of large stature. Most of the teeth showed signs of attrition and were rather worn down.

The life rhythm of the majority of ancient inhabitants in the Sudan and in Malta was consistent with hard work and they probably subsisted on frugal meals without a satisfactory level of nutrition.

A microscopic examination of patterns left by different diets throws light on the nutrition of ancient and later time Man. A largely vegetarian diet requires more mastication and leaves a different pattern of wear than one rich in meat. It is likely that the diet of Neolithic Man in Malta and Gozo seems to correspond to neither a wholly vegetarian nor a meat dependent regime, but tending more to a vegetarian one, perhaps including also a hard element such as seeds, pods, etc.

Obviously, a coarse diet brings about more attrition. Another factor which may be suggested is that the grit which forms in limestone and pottery querns where grain used to be mixed, probably affected the enamel while chewing. Neolithic folk and later communities utilised hollowed stones for milling. The friction generated with a pestle in a mortar resulted in the formation of some grit; that is gradually, particles of stone became incorporated with the milled mixture.

Instruments for grinding grain were found among various other items at the Tarxien Temples. (A. Bonanno and T. Gouder).

According to Dr. T. Gouder, over 50 ancient bodies, many of them disarticulated had been found almost 100 years ago in two chambers at Zebbug. Many teeth showed various levels of attrition.

Normal (average) biting forces: Experiments conducted on adults have shown that the biting force decreases from the molar region to the incisors. Studies have revealed that by and large, biting forces on the first and second molars vary considerably.

It is possible to tell whether human bones belong to young or old males or females.

By the time we stop growing, the ends of the long bones in our arms and legs have fused together. Scientists look for signs of fusion to determine if bones are from a child or an adult.

More information can be obtained from bones. Long periods of malnutrition suffered by children can be detected in their bones and teeth. Wear on bone can indicate that people did particular types of work, such as carrying heavy loads on the back.

Soils affect preservation. Acid soils quickly destroy bone and wood. Luckily not all soils are destructive; bones keep well in chalky soils, oxygen free (anaerobic) conditions.

Dry and oxygen-free (anaerobic) conditions tend to preserve bones. We are now living in a world of expanding medical and scientific knowledge. In Malta and Gozo, as in other countries average life expectancy has improved appreciably over the last century, thanks to a much better lifestyle, better nutrition and better medical and health care. A higher proportion of people die old, perhaps as old as physiology and biology allow. Life expectancy has gradually risen from about the late fifties to around seventy years since 1990. In our times the common causes of death are heart diseases.

On the 23rd July 2008, through the help and courtesy of the Rev. Canon Joe Abela, B.A. (Hons) a Lic. D., I entered the old secret passages within the wide walls near the dome of the Church of St. Gregory at Zejtun, with a view to see the numerous remains of disarticulated bones and skulls of about 50 persons which had been placed there, many many years ago. The reason why they were deposited there is subject to conjecture.

The dome of this historic church had been rebuilt or repaired around 1492. Existing records show that Turks or corsairs landed at Marsaxlokk or nearby in the following years and pillaged the area besides killing and carrying away many inhabitants.

Some old pieces of broken pottery of the 16th – 17th centuries were found.

On entering the unpleasant eerie passages and looking at the numerous disarticulated bones and skills, I felt the atmosphere of gloom and doom and wondered how they came to be there.

My impression of those I saw included the following:

(a) The skulls and bones are not of prehistoric provenance and could probably have been about 450 years old. They had not been in soil previously. With the exception of three, the skulls are dolichocephalous.

(b) Most of them were covered with a layer of dust and a few of the skulls showed cracks. Some showed wear and tear and some teeth showed attrition and caries. Various skulls were of middle-aged persons and one bone showed signs of osteoporosis. A few had almost full sets of teeth. Perhaps they were of younger people.

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Answers to Self-Assessment Quiz
Q1. D, Q2. A, Q3. B, Q4. D, Q5. A, Q6. B C, Q7. A B C, Q8. A C, Q9. A B D, Q10. A B D

Continued Medical Education:
Self Assessment Quiz

The self-assessment quiz contains two types of questions: Type 1 questions have only one correct answer and may have four or five choices. Type 2 questions may have more than one correct answer offering four multiple true-false options.

Type I Questions. Each question has one correct answer.

Q1. Which of the following statements about a patient presenting with testicular pain is correct?

A. Radionucleotide scanning does not give reliable confirmation of the presence of torsion.
B. The patient should be urgently referred to be evaluated by a surgeon/ urologist.
C. Pain may be relieved by scrotal support
D. Surgery should be indicated after ultrasound examination confirms torsion.

Q2. Which one of the following medicines has been shown to decrease mortality rates in patients suffering from type 2 diabetes?

A. Metformin
B. Gliclazide
C. Sitagliptin
D. Rosiglitazone

Q3. Which one of the following is an advantage of casts compared with the use of splints?

A. Easier to apply
B. Provide more effective immobilisation
C. Are better suited for the management of probably unstable fractures in the acute phase.
D. Swelling is less likely to occur

Q4. Which one of the following is characteristically associated with an elevated reticulocyte count during the early evaluation of macrocytosis?

A. Hyperthyroidism
B. Folate deficiency
C. Elevated serum ferritin
D. Haemolysis

Q5. Which of the following statements about therapy outcomes for postmenopausal women is correct?

A. Vitamin D has a lower NNT(number needed to treat) than biphosphonates to decrease the risk of a hip fracture.
B. The Women Health Initiative study confirmed that hormone therapy (estrogen+/- Progesterone) significantly reduced the risk of hip and vertebral fractures.
C. Teriparatide is approved and indicated as a first line treatment for severe osteoporosis.
D. A daily intake of at least 1200mg of calcium and 1000 IU of vitamin D for all women with osteoporosis in not necessarily indicated if they are receiving biphosphonates.

Type II Questions. Each question may have more than one correct answer

Q6. A 38 year old lady complains that she has been feeling unusually tired for the past one to two months. The history and clinical examination do not suggest any cause for her lethargy. Which one of the following diagnostic tests should be considered in the initial investigation?

A. Chest X ray
B. Complete blood count
C. Pregnancy test
D. Peak expiratory flow rate estimation.

Q7. Which of the following should be included in the initial evaluation of patients with symptoms of benign prostatic hyperplasia?

A. Urinanalysis
B. Digital rectal examination
C. Measuring the Prostate-specific antigen levels
D. Evaluating kidney function by serum urea and creatinine measurement.

Q8. Which of the following signs and symptoms is/are seen at presentation in at least one third of patients with primary brain tumours?

A. Headache
B. Papilloedema
C. Memory loss
D. Nausea or vomiting

Q9. Which of the following tests is/are helpful in distinguishing between transient synovitis and septic arthritis?

A. An elevated C- Reactive protein with a level greater than 20mg/L
B. An elevated erythrocyte sedimentation rate greater than40mm/Hr
C. The FABER(Patrick test)
D. A peripheral white cell count greater than 13.0 x 109 /L

Q10. Which of the following is/are treatment options in the management of vitiligo?

A. Sun protection
B. Class III and IV topical steroids
C. Retinoids
D. Ultraviolet light therapy.

Answers on Page 17: After reviewing the answers you may claim 2 CME points by quoting MFD/Dec 2009 CME 002 on your application for accreditation.

Caring for the Diabetic Foot in Primary Care

Anton BUGEJA

Introduction

Non-insulin dependent diabetes mellitus (NIDDM) is a common condition affecting 10% of the world population[1], a further 10-15% of adults aged over 40 years having pre-diabetes and thus carrying an increased high risk of progression to the condition[2]. Major complications in NIDDM are mainly of vascular nature, the renal, ophthalmic, and nervous (peripheral and autonomic) complications arising mainly secondary to microvascular complications while macrovascular pathology being responsible to cerebrovascular, peripheral vascular and coronary heart pathology.

Foot ulcers in diabetics are common and serious[3], and likely to increase in the coming years with increasing incidence of diabetes in the community[4]. As the diabetic foot syndrome leads to amputations, disability and reduced quality of life[5], lower extremity complications in persons with diabetes have become an increasingly significant public health concern in both the developed and developing world.[6] Indeed the prevalence of the diabetic foot varies between 9% to 15% according to the population studied,[7,8] with an estimated annual incidence lying between 1-4% and a lifetime risk of 15%.[9,10] Viewed differently the risk of lower limb amputation in a diabetic is 50-100 times that of the general population[11] claiming about 50% of non-traumatic, lower extremity amputations.[12]

The Public Health impact of these numbers is significant. While in the U.K. this is estimated to cost the NHS around £12.9 million per annum,[13] in the United States an estimated 4% of patients diagnosed with diabetes account for 46% of annual hospitalisations for foot ulcers.[14] Equally of concern is the high mortality of patients with diabetic foot ulcers. Five-year mortality rates in these patients have been reported between 43% and 55%, spiralling up to 74% in patients with lower-extremity amputation. These rates are higher than those for several types of cancer including prostate, breast, colon, and Hodgkin's disease.[15] In patients previously hospitalized with a diabetic foot, mortality is often related to cardiovascular disease. In one study the cause of death was mainly due to acute myocardial ischaemia (24.2%), infection (21.2%) and cerebrovascular accident (10.6%), the prevalence of cardiovascular disease calculated at 70.1%.[16] Thus new-onset diabetic foot ulcers should be considered as a marker for significantly increased mortality and should be aggressively managed locally, systemically, and psychologically.[17]

A number of factors are involved in the development and maintenance of a diabetic foot ulcer. These include polyneuropathy, mechanical overload, peripheral arterial disease and infection.[18] In up to 85% foot ulcers precede amputations in diabetic patients.[19] Since evolution of the disease is slow, it is possible to implement prevention and control measures,[20] but as patient outcomes (such as amputation and death) occur erratically, widespread adoption of auditing this aspect of diabetic care emerges as crucial.[21] Indeed, examination of the feet in a diabetes clinic setting is notoriously known to leave much to be desired,[22,23,24] but good results may be attained if appropriate measures are taken.[25] Despite treatment up to 15% of ulcers fail to heal within 6 months in established specialised ulcer clinics,[26] hence the importance of prevention.

Role of Gp in Management

Proficient in managing chronic diseases, family physicians can work to address this situation. In the Netherlands over 75% of all patients with type 2 diabetes mellitus are being treated by a diabetes team in general practice,[27] while in the United Kingdom over 90% of family doctors provide diabetes care. In the latter setting, strategies in primary care for reducing diabetes related amputations include screening for the foot at-risk, extra review and education for those at risk, and prompt referral to a multidisciplinary foot care team should complications occur.[28]

Despite the available literature, much remains to be done to improve foot care in Malta. In over 140 publications related to Diabetes in Malta, only one article discussed diabetic foot problems,[29] a situation that only improved recently by the publication of an additional article.[30] An audit of type 2 diabetes care at Health Centres failed to include foot care as one of the studied parameters.[31] This situation persists in spite of the fact that the tragic consequences of amputations in Maltese Diabetic patients are well known. In an unpublished study conducted at St Luke's Hospital, 30% of diabetics undergoing amputations were found to die within the first two months of operation, only 50 % surviving after one year.[32] The foreseeable impact on loss of income to families, hospital expenses and loss of life remains unquantified and unaddressed. That there is significant scope for progress in this area is revealed by an audit carried out amongst 28 Maltese doctors from the private and public sector participating on the ICGP Distance Learning

Certificate in Diabetes. Here only 196 (36%) of the 540 patients had their foot examined. Calculated relative to the number of appointments, an average of 0.6 foot examinations per patient were carried out, which together with a 0.49 BMI calculation per patient constituted the worse results of the variables studied.[33] These results are worrying because in the same study 4.4% were recorded as having one or more foot ulcers, 3.14 times the rate recorded in a similar audit carried out in Ireland.[34]

Interventions need to be evidence-based and in line with international standards. The NICE guidelines on the management and prevention of foot problems in NIDDM[35] satisfy these condition by detailing care of the feet (pulses, sensation) and other (smoke, social deprivation) factors that are related and important, also promoting management and education according to assessment of foot risk. A holistic approach needs to be implemented in adopting such guidelines as physicians should also strive to improve function and co-morbidities such as sleep disorders, anxiety, and depression,[36,37] the latter also associated with increased mortality.[38]

Audit Objectives

In line with the above, an audit was performed at the Paola Health Centre Diabetes Clinic to document parameters relevent to the practice of foot care, identify factors that influence its provision and consequently intervene by implementing measures aimed at improving such care.

Method

An audit on diabetic foot care was carried out on clients scheduled to attend the Diabetes Clinic at this Centre during the period 1 March 2008 and 18 April 2008. A total of 397 persons (representing around 25% of the 1556 patients scheduled for appointment in the first six months of the year) were included in the audit. Considering that patients often receive a twice yearly appointment, this percentage approximates the proportion of total patients seen at the relevant clinic. Audit criteria as identified in the NICE guidelines together with others obtained from several clinics related to diabetic foot care were adapted to the local situation and criteria were defined relating to deformity, pulses, foot condition, vibration, risk assessment, referral to podologist, and education provision.[39]

Results and Interventions

First Cycle

The audit population was found to have more males (211, 53.15%) than females (186, 46.85%). Except for 10 patients, all patients were above 51 years of age, the majority (70.28%) in the 61-80 age group. In cases where the relevant data entry existed, it was found that only 19 (4.79%) were on insulin, 265 (66.75%) were on oral hypoglycaemic agents while 113 (28.46%) managed by diet alone. This picture is explained by the fact that the Diabetes Clinic at Mater Dei Hospital usually continues to manage insulin dependent diabetic patients and those below 35 years of age. Only 11 patients (2.77%) enrolled in the first audit cycle had their feet examined. Of these 7 were described as having a good general condition in their feet, a further patient recorded as having dry skin. Six were recorded as having sensation to touch but no record to vibration was recorded. All 11 patients had their pulses recorded; in ten they were described as good while in one patient they were noted as 'weak'. While four patients were referred to a podologist there was no record of any educational advice given. Four were noted to have foot deformity while no deformity was recorded for a further four. Interestingly, one was recorded as having long nails, one had varicose veins and another had an ankle ulcer.

Interventions

When reviewed it was immediately evident that foot examination in the said clinic left much to be desired. Furthermore in cases where feet were examined there was no indication of any foot assessment being done; recorded details were independent of recommendations given in international guidelines. Even from this limited data it emerged that problems were present and that urgent intervention was necessary to implement effective and appropriate diabetic foot care in this clinic. A specially designed single page form was designed for collecting and recording audit data, but also included other parameters that retain it useful in case of future studies. The decision to issue a new form was taken as none of the available diabetic record sheets available at the health centres allowed an appropriate recording of all the criteria identified above and none allowed for risk assessment. Doctors were personally informed that an audit was in place and encouraged to participate. The second audit cycle was launched soon after the MCFD accredited seminar 'Saving the Diabetic Foot' to help boost participation. A purposely made note attached to the notice board of the Diabetes Clinic served as a reminder to all that an audit was in process. After the implementation of the proposed measures was considered complete (end of June 2008), the files of the patients included in the first cycle audit were located and the date of first appointment identified. Review of the files was made on the latter date until the end of December 2008.

Results in Second Audit Cycle

The results of the second audit cycle were as shown in Table 1. Seven patients (1.76%) died between the first and second audit cycle with a mean age at death (72.42 years) that was slightly lower than the life expectancy in the general population.[40] Ten patients (2.52%) had their appointment scheduled for 2009. Forty three patients (10.83%) did not make an appointment by the end of June 2008. A further three made an appointment with other government diabetic departments. Grouped together these 63 patients (15.87%) were unable to have a scheduled second diabetic review at Paola Health Centre for the purposes of this audit. This left 334 patients (84.13%) with a scheduled appointment after the first audit cycle. Seven patients (1.76%) did not turn up. As to the remaining patients, 105 (26.45%) had

a record of a foot examination done while 222 (55.92%) had no note done of any foot examination. Viewed differently, the physician carried out a foot examination on 105 out of the 327 patients attending, or roughly 32%. In view of the lack of local studies available on diabetic foot care, the results of the foot examinations carried out and interventions as outlined in the audit criteria are being illustrated in Tables 3 and 4.

Discussion

This audit has revealed that by appropriately intervening, quality foot care at a diabetic clinic can be improved. The number of examinations recorded to have been performed on attending diabetic patients at Paola Health Centre is now comparable with other primary care settings both locally and abroad, but more remains to be done to provide optimal care for everyone.[41] The relevance and importance of this audit lies in the fact that such examinations are being carried out mainly in a diabetic population which has an age group that coincides with that undergoing the largest number of lower limb amputations in Malta.[42] The magnitude of correctable or manageable risk factors identified within the local diabetic community necessitates a continuous commitment to improve care to such patients. While this study focuses on a single primary care setting the insights gained from this audit can easily be extrapolated to

Table 1: Outcome of patients during second audit cycle

Patients unable to attend second audit cycle at Paola Health Centre Diabetes Clinic	
Died between 1st and 2nd Audit cycle	7
Scheduled for appointment in 2009	10
Scheduled for appointment at another Health Centre	1
Scheduled for appointment at Mater Dei Hospital Diabetes Clinic	2
Patients without appointment by end of June 2008	43
Patients able to attend second audit cycle at Paola Health Centre Diabetes Clinic	
Patient did not attend	7
Note included of foot examination	105
No note was included of foot examination	222

Table 2: Patients identified with foot problems

Foot Problem	Number with problem identified
Foot Deformity	30 (29%)
Pulses	12 (11%)
Skin	27 (26%)
Vibration	19 (18%)

Table 3: Patients with risk factors and management plan adopted
(These numbers indicate that the related management decision was in some cases adopted independent of foot assessment)*

Number of Risk Factors	Number with problem Identified	Number referred to podologist	Number with education given
0	47	55*	69*
1	37	8	11
2	13	4	6
3	7	6	6
4	1	1	1
	Total =105	Total=74	Total=93

other practices. The only way forward is through ensuring that each patient receives a quality assessment of his/her feet at least once a year. By not examining or recording finds, in the above audit the medical profession has emerged as the main limiting factor in the attainment of this goal. Reasons for this situation remain to be determined and studies are needed to evaluate the roles of motivation and physician training within this scenario. Personnel involvement in the audit, degree of practice teamwork, team development of systematic plans to implement change and having a positive attitude to the need to re-audit are all factors that are known to influence audit outcome.[43] In a group practice such as in existence at the Health Centre these changes may be obtained by setting up a diabetic team that is self-directed to achieve positive outcomes and implement strategies for improvement. The development, publication and dissemination of clinical practice guidelines, conduction of training courses, and introduction of a monitoring and evaluation system is an alternative approach that has already contributed to major advances elsewhere.[44]

In a Centre where the medical staff is also required to attend acute cases related to general practice, the minimum time to ensure an appropriate diabetic visit needs to be established and protected. As local studies have revealed that nurse filled parameters are better recorded[45] one may also consider transferring the recording of foot parameters to nurses.[46] Involvement of other staff (such as podologists) and use of shorter recording template may also be beneficial. Even here, the impact of allotting the necessary human resources to such work emerges as a separate complicating issue.

Administrative interventions will hopefully address the lack of foot assessment being carried out in most of the remaining cases, as logistic support is known to improve care processes.[47] A national register of diabetics that informs patient management through established guidelines and which allows for recall of defaulters should go a long way to address this problem. An area-wide, computerised diabetes register incorporating a full structured recall and individualised patient management system has already been shown to yield beneficial results.[48] However, as defaulters may have fewer complications than regular attendees and exhibit a wide range of attitudes to their condition, a specific exercise needs to be implemented as success in attracting back these potential clients is known to be unlikely without major effort.[49]

Evidence based plans should be studied and adopted to streamline the channelling of patients to different members of the interdisciplinary team to bring about improvement in care associated with the latter. Duplication of work may thus be minimised allowing for appointment to be phased at reasonable intervals. The reasons for the number of patients without appointment several weeks after the first audit cycle may be many, but certainly require further study even if clients are known to make appointments at later dates. Inviting patients to submit their views to improve their visit to the diabetes clinic may address this reality. With patients often requiring several other appointments (such as for blood investigations, review by ophthalmologist and podologist) necessary for a complete diabetic review, factors that may benefit the appointment making process should be identified and improved.

Beyond auditing considerations, the results obtained in this audit have highlighted that a considerable number of diabetic patients have an increased risk of foot problems comparable to the picture found in studies elsewhere.[50,51] In itself this should be a significant driving force to implement the necessary changes and organise further studies and audits to assess level of care. In concluding this analysis, one must not loose sight that the NICE guidelines had to be adapted to facilities available locally. The setting up of a Foot Care Protection Clinic reserved for patients in Primary Care remains desirable to provide for regular follow-up in non-urgent cases. An agreed management plan that delivers appropriate patient education remains an important criterion in the NICE guidelines. Thus there is urgent need to introduce education programmes in the near future, as has been highlighted by a recent local study.[52] Brief, individualized educational interventions are known to improve patients' foot care knowledge[53] but need to be repeated to increase efficacy.[54,55]

Conclusions

Foot care is an important aspect of management in the diabetic patient which needs to be developed and adopted further in Malta. Primary care promises to contribute to this field, this audit revealing that changes can be obtained by appropriate interventions. The contribution of every stakeholder is needed as much remains to be done to give to patients the care they deserve.

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Diabetic Dyslipidaemia in Gozo

Association of Glycaemic Control with Dyslipidaemic Patterns and Lipid Target Achievement in Type 2 Diabetics

Bryen GATT, Scott BROWN

Abstract

Purpose:

To determine the frequency with which Type II Diabetes Mellitus (T2DM) patients managed in a primary care setting in the Gozitan community achieved American Diabetes Association (ADA) treatment goals for lipids and whether this was affected by the degree of glycaemic control.

Methods:

A cross-sectional study of 215 randomly selected T2DM patients treated on a primary care level was conducted. Fasting venous blood samples were collected from all patients and analysed for HbA1c, FBG, TChol, HDL and LDL (Friedewald equation). Patients were subdivided into three groups according to glyceamic control: {HbA1c <7% (Good); 7-8% (Satisfactory); >8% (Poor)}. Amongst the three glycaemic control groups, differences in mean lipid levels were evaluated by one-way analysis of variance (ANOVA), and differences in ADA lipid target achievement by Chi squared testing.

Results:

Amongst the three glycaemic control groups, there were significant differences: in all the mean lipid levels (TChol, $p<0.004$; Tri, $p<0.001$; HDL, $p<0.04$; LDL, $p<0.004$) and lipid target achievement for Tchol ($p<0.03$); Tri ($p<0.001$); HDL ($p<0.05$). Frequency of ADA target achievements were: HbA1c (33.9%), TChol (58.6%), Tri (67.9%), HDL(66%), LDL (40%). Frequency of targets at goal: (none = 9.3%; 1 = 16.7%; 2 = 29.3%; 3 = 21.4%; all 4 = 23.3%).

Conclusion:

Better glycaemic control is associated with a significantly better lipid profile for each of the lipid components. The magnitude of this association was sufficient to influence achievement of all individual ADA lipid goals except that for LDL.

Key Words

Type 2 Diabetes Mellitus; Glycaemic control; Diabetic Dyslipidaemia, American Diabetes Association, Primary Care.

Introduction

Background

Gozo forms part of the Maltese Archipelago in the Mediterranean Sea. Diabetic rates of the Maltese population are amongst the highest in Europe[1] with 10% suffering from diabetes as compared to 2-3% of their European neighbours.

Overview of Literature

Lipid abnormalities affect 70-97% of diabetics[2]. Diabetic dyslipidaemia is characterised by a triad of lipid abnormalities including raised Triglycerides (Tri), low High Density Lipoprotein (HDL) and a predominance of the highly atherogenic small dense form of Low Density Lipoprotein (LDL)[3]. There is conclusive evidence that optimal glycaemic control is central to the management of diabetes and the prevention of long-term diabetes-related complications, both micro- and macro-vascular disease[4,5]. Impaired lipid metabolism resulting from uncontrolled hyperglycaemia has been implicated in such complications. There has not been a study analysing whether the degree of glycaemic control has sufficient influence on lipid levels to significantly affect the degree of American Diabetes Association (ADA) lipid goal achievement.

ADA Reco mmended Targets

To improve diabetic control and prevent diabetic complications, the ADA[6] defined the following lipid treatment goals for physicians managing patients with diabetes mellitus: Total Cholesterol (TChol) </=5.2 mmol/l; LDL </=2.6 mmol/l; HDL >1.1 5 mmol/l; Tri

<1.7 mmol/l; and Haemoglobin A1c (HbA1c) <7 %.

The ADA recommended goals were adopted by the study as they have been tailored specifically for diabetic patients, target all the individual lipid components, and already encompass many of the anticipated changes taking place within the European guidelines.

Hypothesis and Study Objectives

The frequency with which T2DM patients are able to attain recommended treatment goals in a primary care setting in Gozo remains to be established. Such data is especially important to primary care physicians who are responsible for providing the bulk of this service.

In T2DM patients, the state of insulin resistance impairs the body's ability to sense glucose in the circulation and consequently leads to a compensatory release of free fatty acids (FFA) from adipose tissue into the blood stream[7]. A high portal FFA concentration has undesirable effects on the liver resulting in hepatic insulin resistance (lipotoxicity), hyperinsulinaemia, hyperglycaemia and dyslipidaemia.

The results of several studies[8,9,10] reflect a causal link between the degree of glycaemic control as a major influence on the level of dyslipidaemia and accelerated atherosclerosis as the ultimate end point. It is postulated that patients with better glycaemic control have a more favourable lipid profile than their counterparts and therefore a better chance of achieving ADA recommended targets.

A cross-sectional study was conducted to determine the frequency with which patients with T2DM managed in a primary care setting in Gozo are achieving ADA treatment goals for lipids and to determine whether the degree of glycaemic control as measured through HbA1c is associated with ADA lipid goal achievement.

The primary objectives of the study were to ascertain:

1) Whether the serum lipid profile in T2DM patients varies significantly amongst the three glyceamic control groups.
2) Whether the three glycaemic control groups have significantly different ADA lipid target achievement rates.
3) The frequency of attainment of ADA recommended lipid targets by T2DM patients in the sample population.
4) The prevailing patterns of dyslipidaemia in T2DM patients living in Gozo.

Methodology

Methods / Procedure

A cross-sectional study was conducted on 215 T2DM patients attending the Gozo Health Centre and Diabetic Outpatient clinic. The study was reviewed and approved by the local research ethics committee and patients gave informed consent. The participants were randomly selected from diabetic registers held at the above institutions using a list of computer generated random numbers. Sample size was determined by power analysis based on a power value of 0.90 and a significance level of 0.05.

The inclusion criteria for the study were:

- Patient type: diagnosed as suffering from T2DM as defined by the WHO (2007) criteria[11].
- Age: between 20 to 80 years of age
- Treatment: stabilised on same lipid-lowering therapy for ≥ 3 months.
- Location: residing in Gozo for the past 12 months.

Patients pertaining to any of the following criteria were excluded:

- Refusing informed consent
- Myocardial infarction, General anaesthesia, or major trauma within 12 weeks prior to enrollment
- Pregnant or breast feeding mothers ≤ 6 months post partum
- Haemolytic disease or significant blood loss
- Renal impairment
- Alcoholism
- On HIV medication, estrogen treatment or taking diuretics.

Recruitment of the participants and data collection took place over a 12 week period extending from September 2007 to November 2007 to avoid major festive activities which could have influenced the study results.

A data input form was completed for each participant consisting of 4 main sections: demographic details, medical history, clinical parameters and clinical lab results.

The medical history section consisted of the participant's drug history, past medical history and relevant family history relating to diabetic/cardiovascular disease in first degree relatives. Relevant diabetes-related complications were abstracted from the patient's medical record. The patient's drug history including diabetic, lipid lowering and cardiovascular risk-reduction medications were also documented.

The clinical parameter section included measurement of the patient's blood pressure and body mass index (BMI). Measurement techniques were standardised and calibrated instruments used.

Venous blood samples were collected after an overnight 12-hour fast using a closed vaccutainer technique and processed the same day at the Gozo General Hospital. The sera were analysed for HbA1c, fasting blood glucose (FBG), Tchol, Tri, HDL and LDL(calculated by Friedewald's equation).

Inter-laboratory and inter-method variability was avoided by having all blood samples analysed at the same quality controlled lab and using the same equipment.

The study participants were subdivided into three groups according to their degree of glycaemic control as indicated by their HbA1c level. A value of <7% indicated good glycaemic control, a value between 7% and 8% indicated satisfactory control, and a value >8% indicated poor glycaemic control.

Statistical Analysis

The data was evaluated by SPSS v.10 statistical package. Missing values were excluded from the analysis.

Descriptive Statistics

Descriptive statistics were performed to compute means, standard deviations, frequencies, and percentages for the demographic variables and for the lipid, blood pressure, body mass index, and HbA1c variables.

Inferential Statistics

Pearson's correlation test was performed to examine various correlations.

The effect of glycaemic control on the mean of various parameters was evaluated by one-way analysis of variance (ANOVA). Values of $p<0.05$ were considered statistically significant.

Table 1: Overall study results.

VARIABLE	TOTAL			MALES			FEMALES			Good Gly Control		Satisf Gly Control		Poor Gly Control		Lipid Rx gp		NO Lipid Rx gp	
AGE (mean, (SD), range)	65.9	9.8	34 to 80	64.1	9.8	34 to 80	67.8	9.5	40 to 80	66.1	8.7	65.2	10.3	64.5	10.1	65.5		66.2	
Number	215			109	50.70%		106	49.30%		73		57		85		91	42.33%	124	57.67%
CLINICAL: (mean, (SD), range)																			
Sys bp	137	15	90 to 180	137	15		137	15		139	17	137	14	136	14	139		135	
Dias bp	78	8	58 to 100	78	8		78	7		79	7	78	8	77	8	78		78	
Weight kg	75.74	11.76	46 to 110	78.27	11.58	54.50 to 110	73.13	11.42	46.00 to 105.50	73.70	11.32	76.06	10.73	77.27	12.64	76.84		74.93	
BMI kg/m^2	30.43	4.74	18.2 to 53.1	29.84	4.43	18.40 to 49.79	31.03	4.98	18.16 to 53.07	29.17	4.66	30.40	3.77	31.53	5.14	30.37		30.47	
Obese	51.6%																		
Over weight	41.40%																		
BIOCHEM: (mean, SD, range)																			
FBG mmol/l	9.77	3.67	3.13 to 31.73	9.64			9.90			7.14	1.38	9.30	1.91	12.33	4.17	9.38		10.05	
HbA1c %	7.98	2.00	4.5 to 14.4	7.76	1.94	4.5 to 14.4	8.20	2.05	4.9 to 13.9	6.11	0.58	7.47	0.30	9.92	1.68	7.89		8.04	
T. Chol mmol/l	5.00	2.30	2.69 to 7.28	4.85	1.17	2.41 to 7.98	5.15	0.92	3.09 to 8	4.71	0.97	4.98	1.02	5.26	1.10	4.6		5.25	
Tri mmol/l	1.56	0.93	0.30 to 6.17	1.66	1.13	0.3 to 6.17	1.45	0.67	0.42 to 3.43	1.25	0.59	1.61	0.89	1.78	1.12	1.6		1.53	
HDL mmol/l	1.28	0.33	0.65 to 2.50	1.22	0.32	0.65 to 2.31	1.35	0.33	0.81 to 2.5	1.36	0.38	1.27	0.32	1.23	0.27	1.49		1.36	
LDL mmol/l	3.00	0.89	0.90 to 5.79	2.86	0.90	1.1 to 5	3.13	0.86	0.9 to 5.79	2.75	0.82	3.00	0.80	3.21	0.95	2.64		3.17	
VLDL mmol/l	0.71	0.42	0.14 to 2.80							0.57	0.27	0.73	0.41	0.81	0.51				
ADA GOAL ACHIEVEMENTS: (#, %)																			
PARTICIPANTS NOT AT ADA GOAL																			
T. Chol	89	41.40%		39	35.78%		50	47.17%		22	30.14%	23	40.35%	44	51.76%	25	27.47%	64	51.61%
Tri	69	32.09%		35	32.11%		34	32.08%		11	15.07%	19	33.33%	39	45.88%	28	30.77%	41	33.06%
HDL	73	33.95%		48	44.04%		25	23.58%		21	28.77%	26	45.61%	26	30.59%	35	38.46%	38	30.65%
LDL	129	60.00%		57	52.29%		72	67.92%		38	52.05%	35	61.40%	56	65.88%	43	47.25%	86	69.35%
PARTICIPANTS AT ADA GOAL																			
T. Chol	126	58.60%		70	64.22%		56	52.83%		51	69.86%	34	59.65%	41	48.24%	66	72.53%	60	48.39%
Tri	146	67.91%		74	67.89%		72	67.92%		62	84.93%	38	66.67%	46	54.12%	63	69.23%	83	66.94%
HDL	142	66.05%		61	55.96%		81	76.42%		52	71.23%	31	54.39%	59	69.41%	56	61.54%	86	69.35%
LDL	86	40.00%		52	47.71%		34	32.08%		35	47.95%	22	38.60%	29	34.12%	48	52.75%	38	30.65%
NONE AT GOAL	20	9.30%		13	11.93%		7	6.60%		2	2.74%	9	15.79%	9	10.59%	8	8.79%	12	9.68%
ALL AT GOAL	50	23.26%		27	24.77%		23	21.70%		23	31.51%	11	19.30%	16	18.82%	27	29.67%	23	18.55%
Number of ADA Targets Not At goal (#, %)																			
1	46	21.40%		27	24.77%		19	17.92%		18	24.66%	12	21.05%	16	18.82%	15.00433	16.49%	20	16.13%
2	63	29.30%		26	23.85%		37	34.91%		24	32.88%	20	35.09%	19	22.35%	23	25.27%	39	31.46%
3	36	16.74%		16	14.68%		20	18.87%		6	8.22%	5	8.77%	25	29.41%	10	10.99%	14	11.29%
4	20	9.30%		13	11.93%		7	6.60%		2	2.74%	9	15.79%	9	10.59%	8	8.79%	11	8.87%
Number of ADA Targets At ADA goal (#, %)																			
1	36	16.74%		16	14.68%		20	18.87%		6	8.22%	5	8.77%	25	29.41%	6	6.59%	26	20.97%
2	63	29.30%		26	23.85%		37	34.91%		24	32.88%	20	35.09%	19	22.35%	23	25.27%	40	32.26%
3	46	21.40%		27	24.77%		19	17.92%		18	24.66%	12	21.05%	16	18.82%	23	25.27%	23	18.55%
4	50	23.26%		27	24.77%		23	21.70%		23	31.51%	11	19.30%	16	18.82%	27	29.67%	23	18.55%
Lipid combination at goal (#, %)																			
total & tri	15	6.98%		8	7.34%		7	6.60%		6	8.22%	6	10.53%	3	3.53%				
total & hdl	4	1.86%		1	0.92%		3	2.83%		1	1.37%	1	1.75%	2	2.35%				
total &ldl	8	3.72%		4	3.67%		4	3.77%		1	1.37%	3	5.26%	4	4.71%				
tri & hdl	36	16.74%		13	11.93%		23	21.70%		16	21.92%	10	17.54%	10	11.76%				
tri & ldl	0	0.00%		0	0.00%		0	0.00%		0	0.00%	0	0.00%	0	0.00%				
hdl & ldl	0	0.00%		0	0.00%		0	0.00%		0	0.00%	0	0.00%	0	0.00%				
total & tri & hdl	19	8.84%		7	6.42%		12	11.32%		7	9.59%	4	7.02%	8	9.41%				
total & tri & ldl	19	8.84%		17	15.60%		2	1.89%		9	12.33%	6	10.53%	4	4.71%				
total & hdl & ldl	7	3.26%		3	2.75%		4	3.77%		2	2.74%	2	3.51%	3	3.53%				
tri & hdl & ldl	1	0.47%		0	0.00%		1	0.94%		0	0.00%	0	0.00%	1	1.18%				
ANTI HYPERGLY AGENTS (%)																			
Diet (no medication)		19.60%			19.00%			20.00%			32.88%		17.07%		9.41%		26.74%		14.16%
1 OHA		36.18%			40.00%			32.00%			45.21%		39.02%		27.06%		40.70%		32.74%
>= 2 OHA		32.16%			31.00%			33.00%			21.92%		29.27%		40.00%		22.09%		39.62%
>=1 OHA and/or insulin		12.06%			9.50%			15.00%			0.00%		14.63%		21.18%		10.47%		13.27%
LIPID LOWERING AGENTS (#, %)																			
Statin	87	40.47%		48	44.04%		39	36.79%		32	43.84%	22	38.60%	33	38.82%				
Fibrate	4	1.86%		0	0.00%		4	3.77%		0	0.00%	0	0.00%	4	4.71%				
Combin of Statin & Fibrate	1	0.47%		1	0.92%		0	0.00%		0	0.00%	1	1.75%	0	0.00%				
On NO lipid lowering treatment	123	57.21%		60	55.05%		63	59.43%		41	56.16%	34	59.65%	48	56.47%				
HbA1c at goal (<7%)	73	33.90%																	
HbA1c at goal (<6.5%)	49	22.79%																	

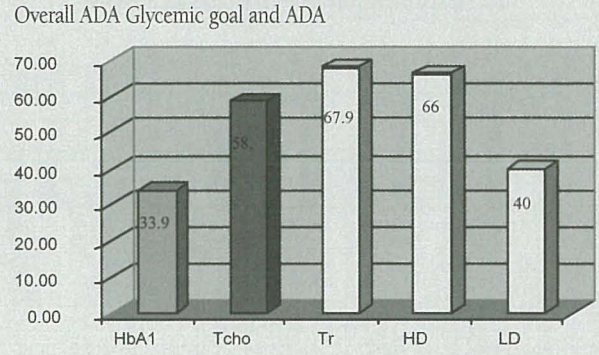
Chi squared testing was employed to analyse ADA lipid target achievement (nominal binary outcome variables) amongst the three glycaemic control groups.

Results & Data Analysis

Overall mean results

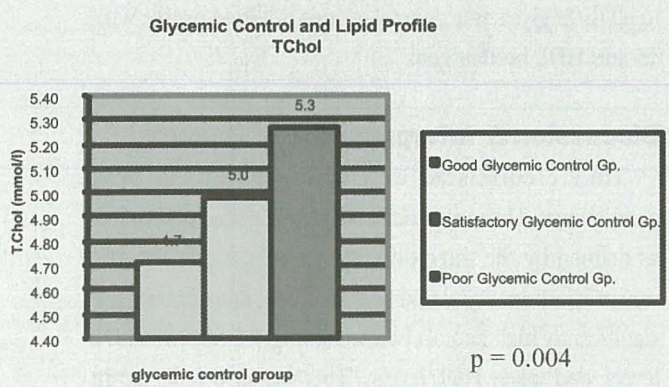
The study data are summarized in table 1. A total of 109 males and 106 females took part in the study with an overall mean age of 66 (+/- 10) years ranging between 34 and 80 years. Overall, study participants were obese with an average BMI of 30.4kg/m^2 ranging from 18.2 to 53.1 kg/m^2 with a mean blood pressure of 137/78 mmHg. Glycaemic control was found to be narrowly satisfactory with a mean (SD) HbA1c of 7.98% (+/-2.00) ranging from 4.5 to 14.4% whilst mean (SD) FBG was 9.8 (+/-3.7) mmol/l. The overall mean (SD) lipid levels of all the study participants were found to be as follows: TChol 5.0mmol/l (+/-2.3), Tri 1.6 mmol/l (+/-0.9), HDL 1.3 mmol/l (+/-0.3) and LDL 3.0 mmol/l (+/-0.9).

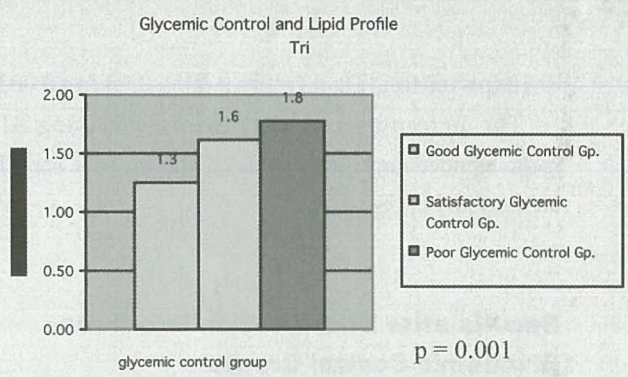
Figure 1: *Overall attainment of ADA recommended targets.*

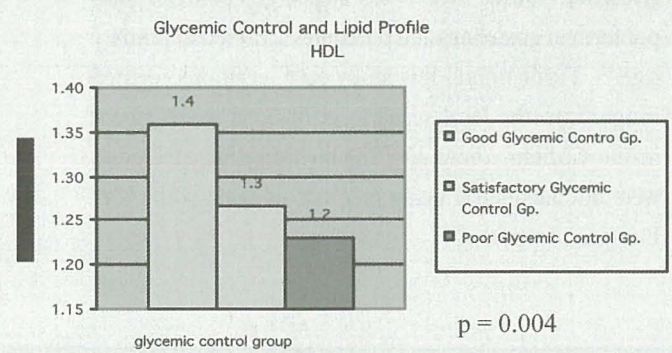


Anaysis using Pearson's correlation coefficient showed that both HbA1c and FBG respectively exhibited statistically significant linear correlations with each of the lipid components: Tchol 0.24 ($p<0.001$), 0.20 ($p<0.001$); Tri 0.19 ($p<0.002$), 0.21 ($p<0.001$); HDL -0.13 ($p<0.029$),

Fig. 2 – *Mean lipid values in Stratified Glycaemic Groups.*







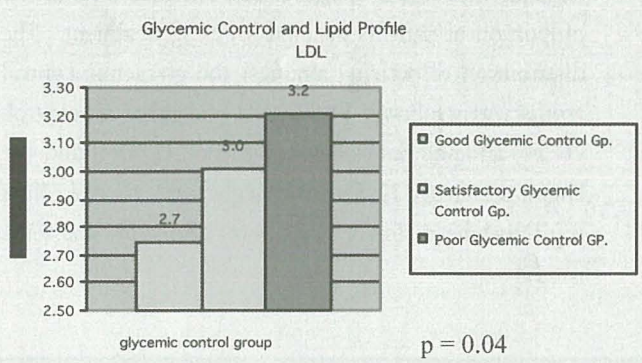


Figure 3: Individual ADA Lipid Goals achieved by glycaemic control groups

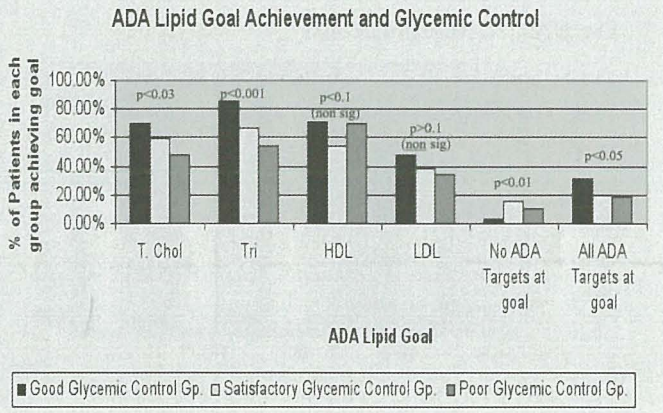
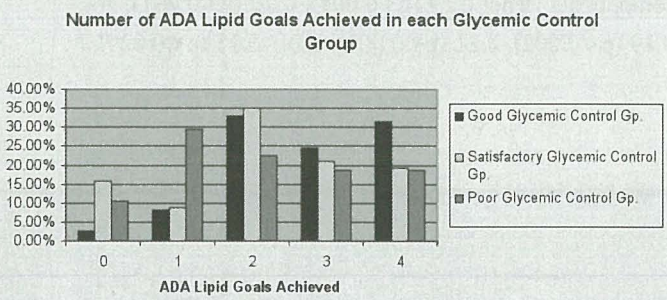


Figure 4: *Number of ADA Lipid Goals achieved by participants in each Glycaemic Control Group.*



-0.12 ($p<0.046$); LDL 0.24 ($p<0.001$), 0.18 ($p<0.003$).

The percentage of participants achieving ADA recommended targets for HbA1c, Tchol, Tri, HDL and LDL are depicted in Fig. 1.

Results after Stratification into three Glycaemic Control Groups

Glycaemic Characteristics

The three glycaemic control groups were similarly matched with regards to age, gender distribution, BMI and proportion of patients on lipid lowering treatment. The distribution of patients amongst the glycaemic control groups was as follows: 34.0% had Good glycaemic control, 26.5% achieved Satisfactory glycaemic control, and the largest percentage 39.5% had Poor glycaemic control. Their respective mean HbA1c levels were 6.1%, 7.5% and 9.9% respectively.

Mean Lipid Values

The mean lipid values in the glycaemic control groups are depicted in the figure below. The difference in lipid levels between the three groups were significant for all of the lipoproteins.

ADA Lipid Target Achievement & Lipid Profile Pattern

The three glycaemic control groups showed different degrees of ADA lipid target achievement as demonstrated in Fig.3.

The number and frequency of lipid goals achieved amongst the three glycaemic control groups is depicted in Fig. 4.

The good glycaemic control group had the highest percentage of patients (31.5%) achieving all four ADA lipid targets. The satisfactory glycaemic control group fared the worst in ADA lipid target achievement with 15.8% of the patients in this group not achieving any of the ADA lipid targets. The lipid profile showed that 76.7% of the patients had at least one lipid value outside the ADA recommended clinical target level whilst 9.3% did not succeed in achieving any of the goals.

The commonest ADA lipid target achievement pattern in all three glycaemic control groups is a lipid profile with Tri and HDL both at goal.

Discussion & Interpretation of Results

HbA1c correlated well with each of the lipid components. The magnitude of impaired glycaemic control as defined by the three different cutoff values of HbA1c was proportionally related with dyslipidaemia in terms of significantly higher total cholesterol, triglycerides, and LDL levels, and lower HDL levels. This was also reflected in ADA lipid goal achievements. Except for LDL, all ADA lipid goal achievement rates were higher in those with better glycaemic control. There was a clear gap between goals put forth in guidelines and outcomes achieved in primary care[12]. Furthermore, this study gave an unprecedented insight into the local scenario of diabetic management in the Gozitan community highlighting that LDL goals were not adequately being met as compared with other European countries.

Aim 1:
Differences in Lipid Profile in Type 2 Diabetes Mellitus Patients According to the Degree of Glycaemic Control

Glycaemic control was associated with significant differences amongst all the lipid components analysed. The better the glycaemic control, the better the associated mean lipid levels (fig. 2). Pearson's analysis demonstrated a highly significant direct correlation between HbA1c and each of the individual lipid levels apart from HDL which similarly showed a directly inverse correlation. Glycaemic control plays an important and significant role in influencing dyslipidaemic levels in T2DM patients and can be a potentially useful tool to improve all the components of diabetic dyslipidaemia. This has practical importance for those components for which there is limited pharmacological assistance such as HDL and Tri. The methods used to achieve glycaemic control can have differential effects on lipid levels beyond their effects on glucose metabolism[13]. This data expands the clinical applicability of HbA1c not only as a reliable biomarker of glycaemic control, but also as an indirect indicator of serum lipid profile in T2DM patients. Patients with impaired glycaemic control have a higher tendency towards having a deranged lipid profile and should be thoroughly assessed for dyslipidaemia and associated complications[14].

Aims 2 & 3:
Association of Glycaemic Control with Ada Lipid Goal Achievement & Frequency of Ada Goal Achievement

Although the magnitude of the effect of glycaemic control on lipid profile has been described to be of limited value by some authors, the current study corroborates what Wagner et al.[15] had concluded from a prospective longitudinal intervention study in that glycaemic optimisation is a useful tool to improve the components of diabetic dyslipidaemia whereby although the effect is individually modest they are globally significant. As seen in Fig. 3, the better the degree of glycaemic control, the higher the achievement rates of all four ADA lipid targets simultaneously ($p<0.05$). Similarly, with improved glycaemic control, there was a significant decrease in the proportion of patients with none of the lipid targets at goal ($p<0.01$). When the effect on individual lipid target achievement was analysed, better glycaemic control was associated with significantly better ADA goal achievements for TChol ($p<0.03$) and Tri ($p<0.001$). The magnitude of this effect appeared to be insufficient to produce a significant increase in HDL and LDL ADA target achievement.

As this may have been partially due to the overwhelming influence of lipid lowering medications on these parameters, patients in the three glycaemic control groups were further subdivided into those on and those not on lipid lowering treatment and the individual lipid profiles analysed to differentiate any pharmacological influence. Chi Squared analysis revealed that in the non-lipid treatment sub-groups, improved glycaemic control was associated with significant differences in HDL goal achievement (5.9, $p<0.05$) and Tri goal achievement (17.9, $p<0.001$), but did not influence LDL goal achievement (1.4, $p>0.05$.).

This may be accounted for due to LDL targets being the most stringent and difficult to achieve as well as LDL levels are mainly altered qualitatively rather than quantitatively in diabetic dyslipidaemia. These results are consistent with findings by Erdman et al.[16] supporting the need for lipid modifying agents to be introduced early in the management of T2DM patients with high LDL levels.

The study revealed that better glycaemic control was associated with higher frequencies of ADA lipid goal achievement. The commonest lipid pattern affecting T2DM patients in the Gozitan community was the achievement of two ADA lipid goals (29.3%) with the most frequent lipid combination being a combination of Tri and HDL both at goal (16.7%). This pattern was most prevalent in the good and poor glycaemic control groups. Standard approaches to managing diabetes will likely benefit HDL and Tri levels even without use of lipid-directed medications.

AIM 4:
Overall Results – The Prevailing Patterns of Diabetic Dyslipidaemia in Type 2 Diabetic Patients in Gozo in Comparison with other Studies

The current study portrayed the local diabetic dyslipidaemia scenario. Overall, the average lipid levels were within recommended ADA lipid targets except for LDL. More than 50% of the T2DM patients studied had achieved ADA recommended treatment goals for TChol, Tri and HDL. Tri levels had the highest ADA goal achievement whilst LDL goal was the most difficult to achieve. Only 40% of patients managed to achieve the ADA recommended treatment goal for LDL. This is low when compared with other European countries which had a 51% achievement rate according to the EUROASPIRE II study[17]. When these values are compared with the proportion of patients

reaching glycaemic goal (33.95%), one finds that there is a higher proportion of lipid target achievement than HbA1c achievement (see Fig. 1). Although only 34% of the study patients were within the established ADA target for glycaemic control (HbA1c<7%), it is comparable to international figures. Studies by the American Diabetes Association[18], The European Diabetes Policy Group[19] and the Canadian Diabetes Association[20] highlighted that over 60% of people with T2DM are still not achieving recommended glycaemic goals despite stringent guidelines for diabetes management.

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Limitations of the Study

- Pertains to a single point in time and limited to community practice settings.
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- No data on patient compliance and on non-pharmacological therapies pursued by patients.

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Funding and Conflict of Interest

None declared.

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Pfizer

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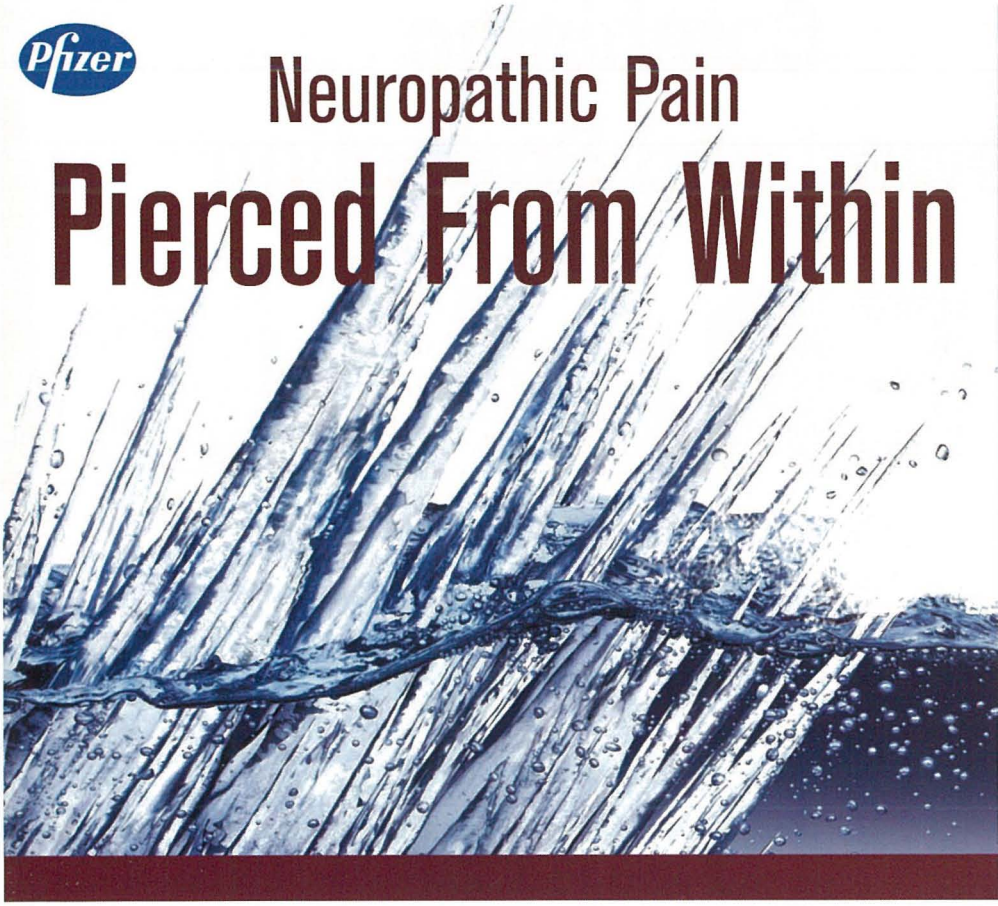

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- Significant efficacy confirmed in 10 double-blind neuropathic pain studies in diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), and spinal cord injury patients[1-3]
- Sustained long-term efficacy in 5 open-label studies of at least 2 years' duration[1]
- 50% or greater reduction in pain reported by up to 47% of patients at highest dose[1]
- No known pharmacokinetic drug-drug interactions[1]
- Simple dosing, with a clear dose-response relationship[1]

LYRICA is indicated for the treatment of peripheral and central neuropathic pain in adults. Despite no pharmacokinetic interactions, LYRICA appears to be additive in the impairment of cognitive and gross motor function when coadministered with oxycodone, lorazepam, or ethanol.

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Abbreviated Summary of Product Characteristics
For additional information please refer to the full Summary of Product Characteristics

NAME OF THE MEDICINAL PRODUCT: LYRICA hard capsules, 25mg/cap, 50 mg/cap, 75 mg/cap, 100 mg/cap, 150 mg/cap, 200 mg/cap, 225 mg/cap, 300 mg/cap. **QUALITATIVE AND QUANTITATIVE COMPOSITION:** Each hard capsule contains 25 mg or 50 mg or 75 mg or 100 mg or 150 mg or 200 mg or 225 mg or 300 mg of pregabalin. Lyrica capsules also contain lactose monohydrate. **PHARMACEUTICAL FORM:** Hard capsule.25 mg capsule: White, marked "Pfizer" on the cap and "PGN 25" on the body with black ink. 50 mg capsule: White, marked "Pfizer" on the cap and "PGN 50" on the body with black ink. The body is also marked with a black band. 75 mg capsule: White and orange, marked "Pfizer" on the cap and "PGN 75" on the body
ink. 150 mg capsule: White, marked "Pfizer" on the cap and "PGN 150" on the body with black ink. 200 mg capsule: Light orange, marked "Pfizer" on the cap and "PGN 200" on the body with black ink. 225 mg capsule: White and light orange marked "Pfizer" on the cap and "PGN 225" on the body with black ink. 300 mg capsule: White and orange, marked "Pfizer" on the cap and "PGN 300" on the body with black ink. **CLINICAL PARTICULARS: Therapeutic indications:** Neuropathic pain: Lyrica is indicated for the treatment of peripheral and central neuropathic pain in adults. Epilepsy: Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
Generalised Anxiety Disorder: LYRICA is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults. **Posology and method of administration:** The dose range is 150 to 600 mg per day given in either two or three divided doses. Lyrica may be taken with or without food. Neuropathic pain: Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval. Epilepsy: Pregabalin treatment can be started with a dose of 150 mg per
after 1 week. The maximum dosage of 600 mg per day may be achieved after an additional week. Generalised Anxiety Disorder: The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly. Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week. Discontinuation of pregabalin: In accordance with current clinical practice, if pregabalin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.8).Patients with renal impairment: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance (see section 5.2), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula.

$$\text{CLcr(ml/min)} = \left[\frac{1.23 \times [\,]}{\text{serum creatinine (}\mu\text{mol/l)}}\right] \quad [\,] = 140 - \text{age (years)} \times \text{weight (kg)} \quad (\times\ 0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
30 - <60	*1	300	BID or TID
≥15 - 30	75 - 50	150	Once Daily or BID
<15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses, BID = Two divided doses, * Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose, + Supplementary dose is a single additional dose.
Use in patients with hepatic impairment: No dosage adjustment is required for patients with hepatic impairment (see section 5.2). Use in children and adolescents: Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).Use in the elderly (over 65 years of age: Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients.
Special warnings and precautions for use: In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications. There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post marketing
advised to exercise caution until they are familiar with the potential effects of the medication. In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (See section 5.1). In the postmarketing experience, visual adverse reactions have also been reported, most of which refer to transient visual blurring or other changes of visual acuity. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms. Cases of renal failure have been reported and discontinuation of pregabalin did show reversibility of this adverse effect. There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin. After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment. Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin. There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse events in general, CNS adverse events and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medication (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.
Undesirable effects: The pregabalin clinical programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.Below all adverse reactions, which
frequency (very common (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The adverse reactions listed may also be associated with the underlying disease and / or concomitant medications. In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse events in general, CNS adverse events and especially somnolence was increased. Additional reactions reported from post-marketing experience are included as Unknown frequency in italics in the list below.
Very Common: Dizziness, somnolence. Common: Appetite increased, euphoric mood, confusion, irritability, libido decreased, ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia, vision blurred, diplopia, vertigo, vomiting, dry mouth, constipation, flatulence, erectile dysfunction, gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema, weight increased. Uncommon: Anorexia, hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia,
postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased, tachycardia, flushing, hot flushes, dyspnoea, nasal dryness, abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral, rash papular, sweating, muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness, urinary incontinence, dysuria, ejaculation delayed, sexual dysfunction fall, chest tightness, asthenia, thirst, blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased. Rare: Neutropenia, hypoglycaemia, disinhibition, elevated mood, hypokinesia, parosmia, dysgraphia, peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness, hyperacusis, atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia, hypotension, hypertension, peripheral coldness, epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring, ascites, pancreatitis, dysphagia, urticaria, cold sweat, rhabdomyolysis, cervical spasm, neck pain, renal failure, oliguria, amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast, anasarca, pyrexia, rigors, pain exacerbated, blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased. Unknown frequency: Hypersensitivity, angioedema, allergic reaction, loss of consciousness, mental impairment, headache, keratitis, congestive heart failure, swollen tongue, diarrhoea, nausea, Stevens Johnson syndrome, Pruritus, urinary retention, face oedema.After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin. **Shelf life:** 3 years. **Supply classification:** POM. **MARKETING AUTHORISATION HOLDER:** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. **LOCAL REPRESENTATIVE OF THE MARKETING AUTHORISATION HOLDER:** V.J. Salomone Pharma Ltd., 79, Simpson Street, Marsa HMR 14, Tel.: +356 21220174. **MARKETING AUTHORISATION NUMBER(S):** EU/1/04/279/001-043.
DATE OF REVISION OF THE TEXT: 03/2008

LYR-MT-2008-07

NEW

Combining Power[1] and Protection[2,3]

COVERAM

5 5 10 10

Perindopril arginine - amlodipine

1 tablet once daily

The only flexible combination in hypertension & stable CAD[4]

Anglo-Scandinavian ascot[2] Cardiac Outcomes Trial

EUROPA[5]

STRONG TRIAL[1]

4 Dosages for 4 advantages

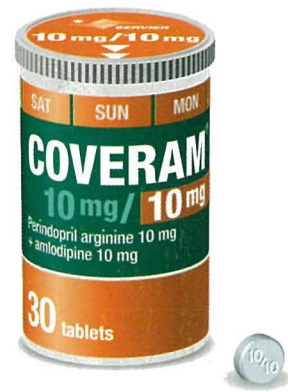
- Powerful blood pressure reduction[1]
- Proven cardiovascular protection[2,3]
- Improve patient compliance[6]
- Flexible prescribing[4]

COVERsyl 5 mg + AMlodipine 5 mg = **COVERAM 5mg/5mg**

COVERsyl 5 mg + AMlodipine 10 mg = **COVERAM 5mg/10mg**

COVERsyl 10 mg + AMlodipine 5 mg = **COVERAM 10mg/5mg**

COVERsyl 10 mg + AMlodipine 10 mg = **COVERAM 10mg/10mg**



COVERAM is also registered under the trade marks: Coverlam®, Coversical®, Covercor®, Covercard®, Reaptan®,Prestance®, Presteram®, Co-Prestarium®, Prestarium-Co®, Prexanor®, Bi-Prestarium®, Coversyl AM®, Calcertil®, Proacertil®, Procoversyl®

Composition: *COVERAM* Each tablet contains perindopril arginine, a long-acting ACE inhibitor, and amlodipine besylate, a calcium channel blocker. Coveram 5 mg/5 mg: one tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine and 6.935 mg of amlodipine besylate equivalent to 5 mg of amlodipine. Coveram 10 mg/5 mg: one tablet contains 6.790 mg of perindopril equivalent to 10 mg of perindopril arginine and 6.935 mg of amlodipine besylate equivalent to 5 mg of amlodipine. Coveram 5 mg/10 mg: one tablet contains 3.395 mg of perindopril equivalent to 5 mg of perindopril arginine and 13.870 mg of amlodipine besylate equivalent to 10 mg of amlodipine. Coveram 10 mg/10 mg: one tablet contains 6.790 mg of perindopril equivalent to 10 mg of perindopril arginine and 13.870 mg of amlodipine besylate equivalent to 10 mg of amlodipine. **Excipient:** contains lactose monohydrate. **Indication:** Perindopril arginine/amlodipine is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given currently at the same dose level. **Dosage and administration:** *Oral route.* One tablet daily, preferably taken in the morning and before a meal. The fixed-dose combination is not suitable for initial therapy. If a change of dosage is required, the dose of perindopril arginine/amlodipine can be modified or individual titration with free combination may be considered. **Contraindications:** *Absolute*: Known allergy to perindopril or to any other ACE inhibitor, history of angioedema associated with previous ACE inhibitor therapy, hereditary or idiopathic angioedema, pregnancy, lactation, severe hypotension, hypersensitivity to amlodipine or to any other dihydropyridines, shock including cardiogenic shock, obstruction of the outflow tract of the left ventricle (high-grade aortic stenosis), unstable angina pectoris, heart failure after acute myocardial infarction during the first 28 days. *Relative*: combination therapy with lithium, potassium salts, potassium-sparing diuretics and certain medicines that cause heart rhythm disorders, estramustine. **Concomitant use to be taken into consideration. Drug interactions:** Diuretics, sympathomimetics, gold, nonsteroidal anti-inflammatory drugs, antidiabetic agents, dantrolene, CYP3A4 inducers (rifampicin, hypericum perforatum, carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), CYP3A4 inhibitors (itraconazole, ketoconazole), beta-blockers in heart failure, baclofen, corticosteroid, tetracosactide, alpha-blockers, amifostine, tricyclic antidepressants, antipsychotics, anesthetics, immunosuppressive agents. **Side effects:** Asthenia, dizziness, headache, mood swings and/or sleep disturbance, cramps, hypotension, allergic reaction, skin rashes, gastrointestinal disorders, dry cough, dry mouth, risk of dehydration in the elderly and in patients suffering from heart failure, blood test abnormalities. **Precautions:** Assess renal function before and during treatment. Renovascular hypertension. Surgery/anesthesia. Renal failure: the dose should be cautiously adjusted in accordance with the creatinine clearance (refer to complete data sheet). Symptomatic hypotension is rarely seen, but is more likely to happen in volume-depleted patients, those receiving diuretics, or with the first two doses. In patients taking diuretics, stop the diuretic 3 days before starting perindopril arginine/amlodipine. A diuretic may be given later in combination if necessary. Potassium-sparing diuretics are not recommended. Patients with impaired hepatic function: amlodipine's half-life is prolonged. Drug should be administered with caution and with close monitoring of liver enzymes. In one third of patients with heart failure, amlodipine was associated with increased reports of pulmonary edema, although there was no significant difference versus placebo. Patients should be treated with caution. Precautions should be taken according to concomitant therapy (ie, drug interactions). KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. **Presentations:** Canister of 30 tablets. Keep the container tightly closed to protect against moisture. Prescribing information may change from country to country. Please refer to the complete data sheet supplied in your country. www.coveram.com

References: 1 - Bahl UK. Fixed dose perindopril and amlodipine in moderate to severe hypertension. 14th World Congress of heart disease 2008, Toronto, Canada. 2 - Dahlöf B. et al. for the ASCOT Investigators. The Lancet 2005; 366:895-906. 3 - Coversyl Arginine 5mg and 10mg Summary of Product Characteristics. 4 - Acerycal Summary of Product Characteristics. 5 - EUROPA Investigators. The Lancet 2003; 362:782-788. 6 - Bangalore S. et al. Fixed dose combinations improve compliance: a meta analysis. Am. J. Med. 2007 Aug; 120(8) :713-9.

Coveram 5mg/5mg: MA066/01501 5mg/10mg: MA066/01502
10mg/5mg: MA066/01503 10mg/10mg: MA066/01504

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