NEWSPAPER POST

TheSynapse
The Medical Professionals' Network

MEDICAL IMAGING

Colorectal cancer

by **Pierre Vassallo**
MD PhD FACA Artz für Radiologie
Consultant Radiologist

Colorectal cancer is the third most common cancer and the second most common cause of cancer deaths in the western world. It occurs with equal frequency in men and women.

Adenomatous polyps are the known precursors of the majority of colorectal cancers, with the risk of malignancy increasing with increasing polyp size. Detection of these polyps followed by polypectomy has been found to prevent the development of colorectal carcinoma. Despite the screening test options currently available, the majority of people who should undergo screening for colorectal cancer do not do so. Four screening tests are routinely used for the detection of colorectal cancer. Current colorectal cancer screening options include faecal occult blood testing, flexible sigmoidoscopy, air-contrast barium enema examination and fiberoptic colonoscopy, whilst a more recently introduced test consists of CT colonography. The faecal occult blood test is safe and inexpensive. However, its performance is poor, since most colon cancers bleed intermittently and most adenomatous polyps do not bleed. The sensitivity of the faecal occult blood test as a single test for colorectal cancer is 20%–30% and for a large polyp is 10%–15%. The sensitivity of this test for colorectal cancer increases with repeated screening and ranges between 72% and 78%. Many causes of false-positive results exist, such as upper gastrointestinal tract sources of bleeding. However, randomised controlled trials have shown that the faecal occult blood test confers a 15%–33% mortality reduction from colon cancer.

Flexible sigmoidoscopy allows examination of about 60 cm of the colon, and therefore only 40%–65% of lesions are within reach of the sigmoidoscope. Up to 50% of proximal cancers are not associated with a distal index polyp. A recent study in 2,885 patients showed that a combination of faecal occult blood testing and flexible sigmoidoscopy failed to detect 24% of cases of advanced colorectal cancer. However, periodic sigmoidoscopy has been shown to reduce colorectal cancer mortality by 60%–80%.

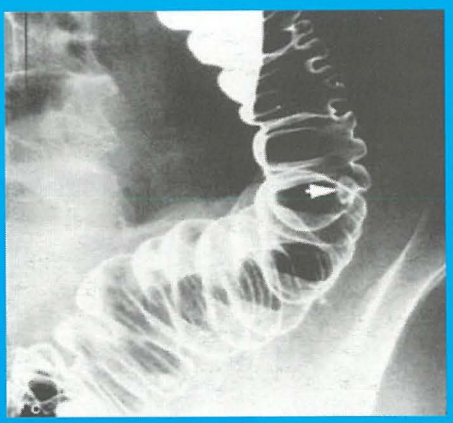

Figure 1. *Barium enema showing a small adenomatous polyp.*

Double-contrast barium enema examination has been found to have sensitivities ranging from 71% to 95% in the detection of colon carcinoma (Figure 1) in retrospective studies and is generally considered to be an excellent test for the detection of clinically significant lesions. However, the sensitivity decreases with polyps (Figure 2) and adenomas smaller than 10mm in diameter.

Fiberoptic colonoscopy is considered the gold standard for colon evaluation (Figures 3 and 4). However, colonoscopy has also been found to miss polyps with a miss rate of 24% for adenomas overall, 27% for adenomas 5 mm in diameter or smaller, 13% for adenomas 6–9 mm in diameter, and 6% for adenomas 10 mm in diameter or larger. Other limitations of colonoscopy include extremely variable patient compliance, the need for multidrug intravenous sedation, and the high cost of the test. In addition, the procedure is time-consuming and is incomplete in up to 10% of cases due to colonic anatomy (long or very tortuous colon).

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Editor's Word

Welcome to the third issue of The Synapse Magazine for 2007. Once again, this issue of the magazine is packed with interesting articles submitted by fellow colleagues. Apart from the regular contributions on radiology and avian influenza, you will also find articles on *Pharmacogenetics – promise for the future?*, *Obesity and Cardiometabolic risk*, *The Human Papilloma Virus Vaccine – The Do's and Don'ts*, the third and last part of *Invertebrates in the medical service of man* and the first part of an article discussing the controversial topic – *Data Protection Act*. Furthermore the magazine is also launching a series of contributions on psychiatry and stress management. The first two articles which will feature in this issue will discuss *Exercise and Major Depressive Disorder* and *Psychiatric Nursing, the evolving role in mental health*.

We also proudly introduce the third set of interviewees for this year Dr Mary Rose Cassar and Dr Anna Spiteri who are the first two female registrars in the Casualty Department of St Luke's Hospital and founder members of the Malta Resuscitation Council.

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Editor: Dr Wilfred Galea
Scientific Editor: Ian. C. Ellul
Designer: Conrad Bondin

Colorectal cancer

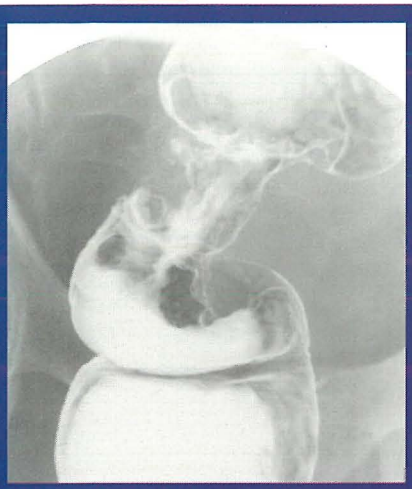


Figure 2. *Barium enema showing a cancer of the rectosigmoid junction with luminal stenosis.*

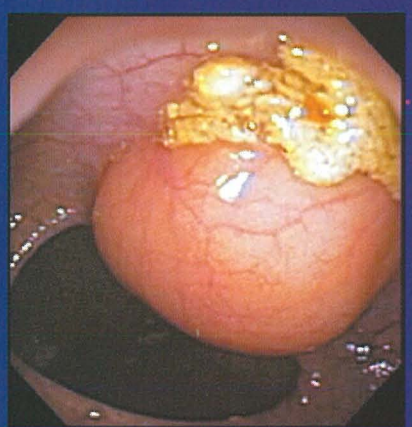


Figure 3. *Conventional colonoscopy showing an adenomatous polyp.*

CT colonography was first introduced in 1994 and has received widespread attention as a possible screening tool for colorectal polyps and cancer that may help to increase the rate of patient compliance. CT colonography involves the use of spiral CT data in combination with advanced graphical software to generate two-dimensional views and three-dimensional endoluminal views of the colon (Figure 5), which may be viewed dynamically and interactively on a computer workstation to simulate a conventional colonoscopy.

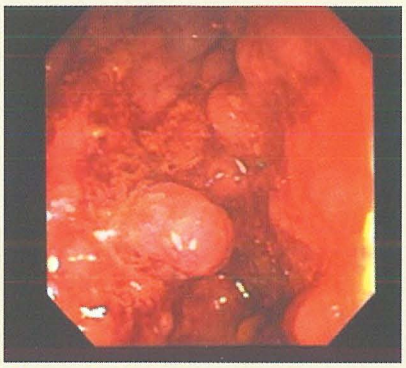
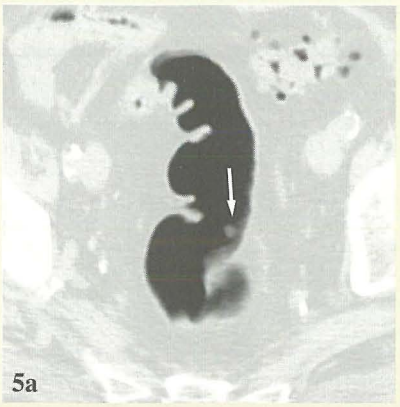


Figure 4. *Conventional colonoscopy showing an en plaque infiltrating colonic cancer.*

Adequate colonic preparation and distension are necessary to ensure maximal diagnostic quality and patients must still undergo a colonic cleansing regimen before CT colonography. CT colonography and conventional colonoscopy have been shown to have equivalent sensitivity in the detection of the 10-mm-diameter or larger polyps that are considered to be clinically significant. CT colonography has been found useful in the evaluation of the colon proximal to a lesion that is causing distal obstruction (Figure 6) and in the setting of failed colonoscopy. Several published studies have documented the ability of CT colonography to show the cause of obstruction, as well as to depict additional cancers and polyps in the colon proximal to the distal lesion.

The advantages of CT colonography are that it presents minimal risk to patients, has a short procedure time (about 10 minutes), can be performed in patients with distal occluding lesions, and can be used to localize lesions more precisely than with colonoscopy. CT colonography also allows diagnosis of extracolonic findings and screening for other clinically important diseases.



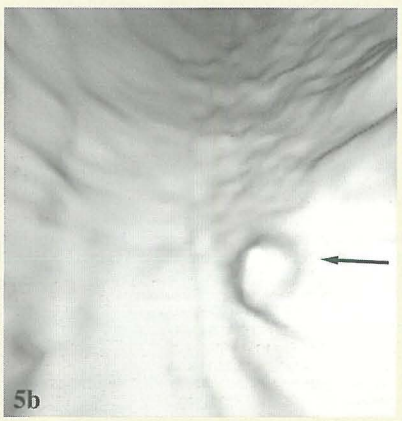


Figure 5. **(a)** *Axial CT scan shows a small polyp (arrow) in the sigmoid colon.* **(b)** *Three dimensional endoluminal view shows the same polyp (arrow).*

Moderately significant findings such as gallstones, as well as highly significant findings such as renal cell carcinoma, large abdominal aortic aneurysms, and liver and adrenal masses can be identified.

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Catafast 50 mg powder for oral solution
Presentation: Diclofenac potassium: powder for oral solution in sachets of 50 mg. Indications: Short-term treatment in the following acute conditions: post-traumatic pain, inflammation and swelling, e.g. due to sprains, post-operative pain, inflammation and swelling, e.g. following dental or orthopaedic surgery, painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis, migraine attacks, painful syndromes of the vertebral column, non-articular rheumatism, as an adjuvant in severe painful inflammatory infections of the ear, nose or throat. **Dosage:** Dose to be individually adjusted, lowest effective dose to be given for the shortest duration. Adults: 50 to 150 mg daily in divided doses. For dysmenorrhoea and migraine attacks: up to 200 mg daily. Adolescents aged 14 and over: 50 to 100 mg daily in divided doses. Not recommended in children and adolescents below 14 years of age. **Contraindications:** Active gastric or intestinal ulcer, bleeding or perforation; known hypersensitivity to diclofenac or to any of the excipients, to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs); last trimester of pregnancy; severe hepatic, renal or cardiac failure. **Precautions /warnings:** Avoid use with other systemic NSAIDs including COX-2 inhibitors. Risk of gastrointestinal (GI) bleeding, perforation or serious allergic reactions; to be discontinued if these conditions occur. Risk of allergic reactions. May mask signs and symptoms of infection. Caution recommended in patients with symptoms/history of GI disease, asthma, seasonal allergic rhinitis, chronic pulmonary diseases, elderly or impaired hepatic function (including porphyria), ulcerative colitis or Crohn's disease. Caution when used concomitantly with corticosteroids, anticoagulants, anti-platelets agents or SSRIs. Caution while driving or using machines. Should not be used in the first and second trimester of pregnancy and by breast-feeding mothers. Not recommended to use in women attempting to conceive as it may impair female fertility. Combined use with protective agents to be considered in patients with history of ulcer, elderly, and those requiring low dose aspirin. Monitoring of liver function and blood counts recommended during prolonged period. Monitoring of renal function recommended in patients with history of hypertension, impaired cardiac or renal function, extracellular volume depletion, the elderly, patients treated with diuretics or drugs that impact renal function. Monitoring recommended in patients with defect of haemostasis. As Catafast contains a source of phenylalanine, may be harmful for patients with phenylketonuria. Beware of severe fluid retention and oedema. **Interactions:** Caution with concomitant use of diuretics and antihypertensives (e.g. beta blockers, ACE inhibitors), methotrexate, other NSAIDs and corticosteroids, SSRIs. Monitoring recommended for patients receiving anticoagulants, anti-platelet agents as well as blood glucose level if used concomitantly with antidiabetics. Monitoring of serum lithium and digoxin levels recommended if used concomitantly. Dose of diclofenac to be reduced in patients receiving ciclosporin. Interactions with concomitant use of quinolones antibacterials. **Adverse reactions: Common undesirable effects are:** Headache, dizziness, vertigo, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, transaminases increased, rash. **Rare undesirable effects are:** Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock), somnolence, asthma (including dyspnoea), gastritis, gastrointestinal haemorrhage, haematemesis, melaena, diarrhoea haemorrhagic, gastrointestinal ulcer (with or without bleeding or perforation), hepatitis, jaundice, liver disorder, urticaria, oedema. **Very rare undesirable effects are:** Thrombocytopenia, leukopenia, anaemia (including haemolytic anaemia and aplastic anaemia), agranulocytosis, angioneurotic oedema (including face oedema), disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, visual disturbance, vision blurred, diplopia, tinnitus, hearing impaired, palpitations, chest pain, cardiac failure, myocardial infarction, hypertension, vasculitis, pneumonitis, colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis, fulminant hepatitis, bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus, acute renal failure, haematuria, proteinuria, nephritic syndrome, interstitial nephritis, renal papillary necrosis. 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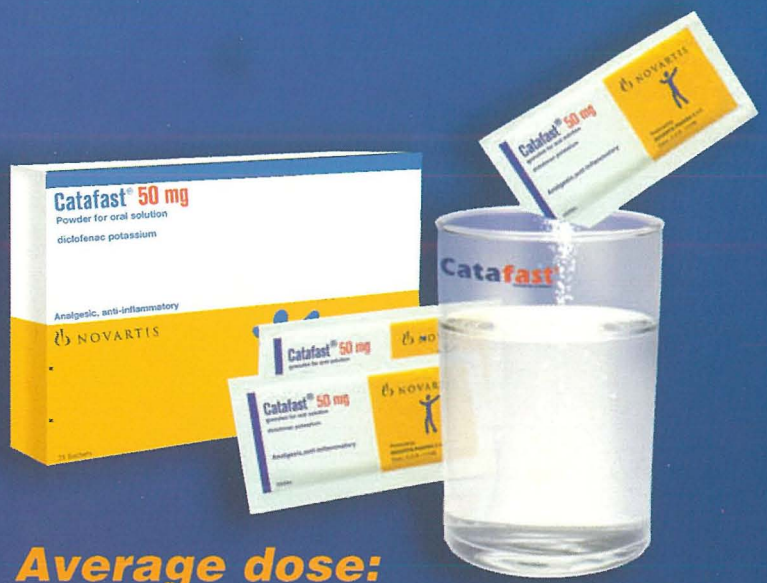

Average dose:
2-3 sachets/day

- **Onset of action within 5 minutes** [1]
- **Significant pain relief within 13.5 minutes** [2]
- **Placebo-like tolerability** [3]

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Pharmacogenetics – p

by **Anthony Fenech**
BPharm(Hons) MPhil PhD(Nott.)
Department of Clinical Pharmacology and Therapeutics
University of Malta

Current and future developments in pharmacogenetics and pharmacogenomics have often been cited in the scientific literature to be the path towards personalized prescribing, allowing for individualized optimization of therapeutic efficacy and minimization of adverse drug reactions. Further research coupled with the establishment of sound ethical guidelines may soon allow pharmacogenetic DNA testing to become part and parcel of standard clinical practice.

Introduction

The term 'pharmacogenetics' first appeared in the scientific literature in 1959.[1] It was coined by Friedrich Vogel, and he used it to refer to the influence of genetic factors on the response to drugs. The existence of inter-patient variability to drug responses had long been recognised for several years, but it is only recently with the help of advances in molecular genetics, that science has began to unravel the secrets within our genome that may contribute to this variability.

Pharmacogenetics or pharmacogenomics?

The advent of large scale, high throughput molecular research, has brought with it new terminology. While the meaning Vogel assigned to 'pharmacogenetics' has been traditionally maintained, a newer term, 'pharmacogenomics', is used to describe the study of whole genomes, or large numbers of genes relevant to drug response at a cellular, tissue, individual or population level. Such pharmacogenomic approaches have a role in the identification of novel putative drug targets, and in the study of the influence of drugs on the expression of a large number of genes.[2,3]

Pharmacogenetic variation

There is a rapidly growing list of genetic polymorphisms which are being recognised to influence drug responses. Such variations have been identified in both coding and regulatory regions for genes which encode drug metabolizing enzymes, receptor proteins, drug transporter molecules as well as other proteins which are involved in the pharmacological pathway of the drug in question.[4] Some examples will be treated below.

Mercaptopurine is predominantly inactivated by the enzyme thiopurine S-methyl transferase (TPMT). About 10% of the population is heterozygous for the TPMT gene, and carry an allelic variant that is incapable of producing functional TPMT enzyme, while 0.3% is homozygous for the mutant alleles and are not capable of producing any functional enzyme. Patients with low TPMP activity and who are treated with mercaptopurine accumulate excessive concentrations of active thioguanine molecules in blood cells, leading to potentially severe haematopoietic toxicity. Indeed, homozygous mutant individuals only require 5-10% of the conventional doses for successful treatment.[5,6] CYP2D6, a member of the Cytochrome P450 family, is responsible for the metabolism of several pharmacologically unrelated drugs, including antidepressants, codeine and beta-blockers, while CYP2C9 is responsible for the metabolism of NSAIDs, warfarin, tolbutamide and phenytoin. Functional variants of the genes for these enzymes, which result in the production of altered enzymatic activity have been identified. Patients inheriting these variants, show altered pharmacokinetic profiles to these drugs, resulting in either potentially toxic blood levels or low blood concentrations of the active drug which would be conducive to decreased therapeutic efficacy.[7,8,9]

Gene promoter variants may potentially influence the rate of transcription of a particular gene, and therefore the level of expression of the protein product. Specific polymorphic variation within the promoter regions of the gene coding for the 5-lipoxygenase enzyme (ALOX) has been associated with non-response to zafirlukast, a cysteinyl leukotriene-receptor antagonist drug used in the management of bronchial asthma. Asthmatic patients carrying this ALOX promoter variant, would therefore not benefit from this drug.[10,11]

Beta-2 adrenoceptors are G-protein coupled receptors which are primarily expressed on airway smooth muscle cells and constitute the target for beta-2 agonist bronchodilator drugs such as salbutamol, terbutaline, formoterol and salmeterol. Nine single nucleotide polymorphisms have been identified in the beta-2 adrenoceptor coding region, of which 4 result in amino acid substitutions at the protein level. Two of these have been shown to be functionally relevant. One variant, for which the sixteenth amino acid is glycine instead of arginine (Arg16–>Gly), has been shown to downregulate faster in the presence of agonists,[12] and indeed patients who are homozygous for Gly16 have been shown to develop tachphylaxis to formoterol treatment faster than patients who carry the Arg16 variant.[13] A second polymorphism (Gln27–>Glu) confers on the receptor a strong *resistance* towards agonist-promoted desensitization and downregulation.[14] The results of this effect have been observed both *in vitro* as well as *in vivo*.[15]

Personalized patient prescribing

The aim of pharmacogenetic research is to eventually develop DNA testing procedures that will enable a prescriber to predict a patient's response to a particular drug in terms of efficacy as well as predict the potential for development of particular severe adverse drug reactions. This approach aims to select the right medicine for the right patient, and would be expected to revolutionise treatment outcomes with positive impacts on health quality and costs.[16,17] The development and eventual commercial availability of 'bedside' pharmacogenetic tests introduces a hitherto undetermined new cost-factor into the pharmacoeconomic picture. This should not adversely tip the scales of the cost-benefit ratio.

It might eventually become relevant to pharmacogenetically stratify volunteers participating in clinical trials, in order to gain a better understanding and assessment of drug efficacy in specific genetically defined patient populations. Pharmaceutical companies may be provided with a niche market, for the development of new drugs for specific use in patients who are

romise for the future?

pharmacogenetically compromised with respect to currently available therapy. However financial viability remains a variable in this equation.

Ethical issues

The future availability of pharmacogenetic testing for specific drugs is not devoid of ethical dilemmas. A pharmacogenetic test might reveal more knowledge than is specifically intended. For example, a patient who is a rapid metabolizer for a particular drug, is likely to also rapidly metabolize other pharmacologically unrelated drugs which share the same metabolic pathways. Should such additional information be disclosed to the patient? In the clinical setting, a patient might be expected to provide informed consent for a pharmacogenetic test to be carried out. The implications of such a test should be clearly explained, and the result should be accompanied by professional advice. Ethnicity may bear an influence on the validity of a pharmacogenetic test, since specific genotypes may only be present in particular populations. Will test developers take this into account, or will particular populations be sidelined due to marketing or financial considerations? It is possible that pharmacogenetic information may be requested by insurance companies, to aid in the computation of health insurance premiums, thus potentially dissuading patients from consenting to such tests for fear of having to pay higher premiums or being unable to obtain insurance. It is applaudable that the UK imposed a moratorium on the use of genetic and pharmacogenetic data for setting insurance premiums. This moratorium however expired in 2006.[2,18]

Conclusion

Although rapidly expanding, it is debatable whether the current status of available pharmacogenetic data is sufficient to justify routine genotyping of all patients prior to initiation of any specific pharmacological treatment. However, as new genetic data becomes available, and novel therapies are developed, the knowledge of patients' genotypes will be a necessary requisite in order to enable pharmaceutical companies and prescribers to optimize management of a disease. Further clinical and molecular work is needed in order to consolidate and expand current knowledge, and a search of the scientific literature databases will show that such work is rapidly advancing forward. The present status suggests that pharmacogenetic testing for specific drugs may be available sooner rather than later.[19,20] The importance of this area of research has been accented by the recent UK Department of Health announcement of a commitment of £4 million over 3 years to be granted to pharmacogenetic research.[2]

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The gastrointestinal safety profile of Prexige® – a new COX-2 inhibitor

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COX-2 inhibitors were developed to reduce the incidence of life-threatening gastrointestinal side effects seen with non-selective NSAIDs.[1]

The gastrointestinal (GI) safety profile of Prexige, a new COX-2 inhibitor, was examined as part of TARGET, the largest osteoarthritis outcomes study ever published.

The TARGET study

TARGET was a multi-national, double-blind, randomised, parallel-group, 52 week study in patients with OA. (*see Table*).[1]

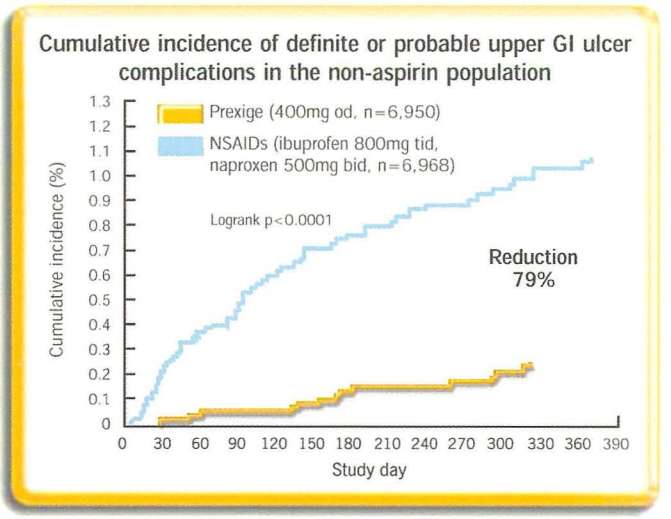
TARGET

Therapeutic Arthritis Research and Gastrointestinal Event Trial

- 18,325 patients. Mean age 63yrs. 76% female
- Reflected a 'real life' OA population
  - 24% were taking aspirin in addition to study medication
  - Patients had a range of concomitant conditions
- Compared Prexige 400mg od (supratherapeutic dose) with naproxen 500mg bid and ibuprofen 800mg tid
- Primary GI endpoint was upper GI ulcer complications (bleeding, perforation or obstruction) in the non-aspirin population

GI results from TARGET

In this trial, the rate of perforation, obstruction or bleeding, the primary endpoint, was significantly reduced by 79% vs the NSAIDS ibuprofen and naproxen in the non-aspirin population.[2]



Adapted from reference 2

The reduction in the rate of perforation, obstruction or bleeding seen in other populations in TARGET was:[2]

- 66% in the overall population (p<0.0001)
- 21% in the aspirin population (p=0.4876)

Prescribing Prexige

Use 100mg od for the symptomatic relief of OA of the hip and knee.

Cardiovascular (CV) outcomes for Prexige have been studied for up to 12 months only, and it is impossible to exclude the possibility that CV risk increases with duration of use. COX-2 inhibitors, including Prexige, are contraindicated in patients with established ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and/or moderate-to-severe heart failure (NYHA II-IV). Patients (especially those taking low-dose aspirin, for whom there is no clearly established GI benefit) with significant risk factors for cardiovasular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with COX-2 inhibitors after careful consideration. The lowest effective dose of COX-2 inhibitors should be prescribed for the shortest duration necessary and patients' need for treatment should be reassessed periodically.

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Exercise and Major Depressive Disorder

by **Kirill Micallef-Stafrace**
MD MSc Sports Med (Lond.) FFSEM (RCSI & RCPI) FFSEM (UK)
Sports and Exercise Medicine Specialist

The World Health Organisation has identified mild to moderate Major Depressive Disorder (MDD) as ranking behind Ischaemic Heart Disease for years of life lost due to disability or premature death.

Although a number of effective pharmacologic and psychotherapeutic treatments for MDD have been developed, many people do not seek treatment or do not receive adequate treatment. Within this scenario a niche does exist for new treatment approaches that will accommodate the diverse needs and preferences of potential sufferers and yet take into account the limited resources of current healthcare systems. Exercise might be one of these new treatments that can provide a cost effective stratagem and, in some cases, maybe even a solution.

In 1999 Lawlor and Hopker reviewed 14 studies that reported the beneficial effects of exercise on MDD and even proposed its effectiveness to be equivalent to cognitive therapy. However, as they rightly pointed out, many of the studies reviewed exhibited flawed research methodologies. Yet this review probably inspired the large number of higher quality investigations that have surfaced in recent years. These studies irrefutably show that subjects suffering from MDD who undertook regular exercise had a greater improvement in their condition than non-exercising control subjects. What is more interesting is that even after exercise was stopped the anti-depressant effect was felt for months after. Thus, these newer studies upheld the results of the pre-2000 research, that exercise has a significantly beneficial effect on symptoms of depression. Also, one must not forget the various health benefits a patient can reap if he/she undertakes regular exercise, thereby tackling the co-morbidities commonly found in depressed patients.

Obviously, exercise must be used as an adjunct to conventional therapy and should be undertaken cautiously, especially if the subject is new to exercise or has not exercised for some time. From a health perspective, exercise is ideally practised most, if not all days of the week, for a minimum of 30 minutes each time. Aerobic forms of exercise such as running, cycling and swimming, appear to have better results in MDD and if this is the primary reason for referral, health professionals should strive to prescribe these activities.

Health professionals, who work with depressed patients, know that one of the major stumbling blocks is motivating the subject. This is no different with exercise and, thus, the chosen exercise must be tailored to the patient and must reflect preferences and accessibility. Some will thrive in individual sports whilst others would require a group exercise setting in order to achieve results.

Whatever the form of exercise chosen, the health professional is integral to the success of the whole scheme. Regular input and encouragement is a must if the therapeutic exercise is to succeed. Familiarisation with the different forms of exercise available to the patients, although not necessary, is a definite bonus. The ability to speak the jargon and communicate in exercise terms with both trainers and patients can break down a number of obstacles before they even appear and smoothen the whole process, thereby increasing the chances of success.

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On Data Protection Act – Part I

by **Pierre Mallia** *MD MPhil PhD FRCGP*
Director, Centre for Bioethics, c/o Molecular Genetics, Medical School

My past experience as President of the Malta College of Family Doctors has taught me how much doctors try to interpret the law; especially when it comes to EU directives in relation to medicine. This is quite understandable. Yet if the cautiousness of lawyers had never taught me anything, my other experience on a fifth framework project, PRIVIREAL[A], which dealt with the EU directive on Data Protection as applied to medicine and in particular DNA, has taught me even more how tricky it can be to try to interpret the law. I was privileged to work with over sixty lawyers from different EU states, and they were all humble in their dealing with laws. They treated the law with the respect with which we treat our patients – no hasty interpretations.

I am certainly no expert, but along with those who went into some detail regarding Data Protection, I have seen myths being created that perpetuate into illegality. Data Protection laws are there to protect the fundamental rights and freedoms of the individual. The EU directive on Data Protection *is not*. It takes for granted that EU states do indeed protect fundamental rights and freedoms[1]. In itself the directive is in fact wrongly often referred to as the 'privacy act', which it is not. In fact, the directive is there to facilitate transfer of information between EU states. The raison d'etre of the EU is to do away with economic barriers, and this is what the directive is all about. It is primarily not concerned with medicine, but takes medicine, statistics and historical matters to task as well. The fact that it gives exemptions to medicine, does not mean that privacy does not exist when it comes to doing research on samples. This is what PRIVIREAL was all about. It simply means that doctors can make use of files to treat patients.

Data Protection laws are there to protect the fundamental rights and freedoms of the individual. The EU directive on Data Protection ***is not***

Therefore, the act in itself is there to prevent us from impeding transfer of information within EU states. Even if we feel that a country does not protect data sufficiently, it is this act which stops us from not allowing information transfer. Protests can only be done through the EU itself. The Data Protection Law in Malta conforms to the Directive.[2]

Data protection laws within EU states vary in their degrees of definition of what is a person. Some would include the fetus and dead people, others only seem to imply it, whilst others directly exclude these criteria. Also, there seems to be divergent views of definitions such as anonymity. One myth is that once something is anonymised, then one can do what one wishes with the data. But if someone has the key, or a reference, to which we can go back to find the subject, even if it is not the researcher himself, then this data cannot be considered anonymous.

Conversely Recital 26[3] of the directive allows for individual control even of anonymized data. A person has a right to disallow his or her data to be used for research to which they would have moral objection to. In this regard the directive does not allow broad consent to samples being used for research purposes. Informed consent imposes that we would still have to go back to patients to explain what the research is all about. This has been hard to digest by the medical profession, which has a considerable amount of samples stored over the years. However, the directive seems to allow an exception where this is not feasible – such as using samples obtained before the local act was adopted, where it would be difficult to trace the individuals to obtain their consent. However, the Data Protection Commissioner would have to give his approval; which may be done through a Research Ethics committee that he allocates for the purpose.

Footnotes

A. Acronym for 'Privacy in Medical Research and Law', PRIVIREAL is a European Commission funded project examining the implementation of Directive 95/46/EC on data protection in relation to medical research and the role of ethics committees in European countries. The project is co-ordinated by Prof. Deryck Beyleveld, Faculty of Law, University of Sheffield.

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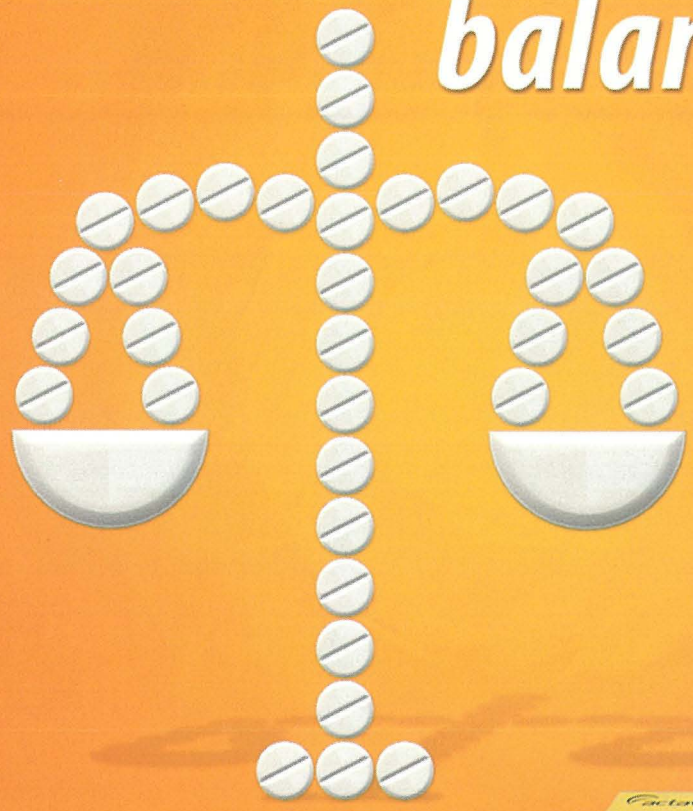

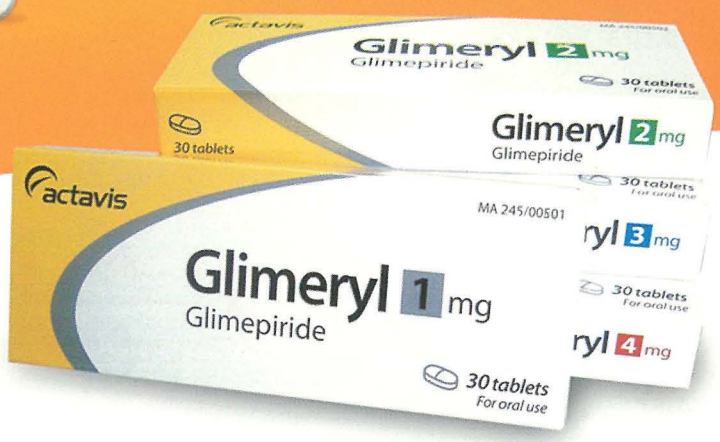

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In patients not adequately controlled with the maximum daily dose of Glimeryl, concomitant insulin therapy may be initiated if necessary. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. It is recommended that this dose be taken shortly before or during a substantial breakfast. If no breakfast is taken, the dose should be taken shortly before or during the first main meal. During the course of treatment, there is an improvement in the control of diabetes due to higher insulin sensitivity. Thus, glimepiride requirements may fall. To avoid hypoglycaemia, timely dose reduction or cessation of therapy must therefore be considered. Change in dosage may especially be necessary, if there are changes in the weight or life style of the patient, or other factors that contribute to the risk of hypo-or hyperglycaemia. **Contraindications:** Insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal and hepatic disease, known hypersensitivity to glimepiride, other sulphonylureas or other sulphonamides or hypersensitivity to any of the excipients in the tablet. **Special warnings and precautions for use:** When meals are taken at irregular hours and especially if meals are omitted, treatment with Glimeryl may lead to hypoglycaemia. Treatment with Glimeryl requires regular monitoring of glucose levels in blood and urine. In addition, determination of the amount of glycosylated haemoglobin is recommended. Regular haematological monitoring (especially leucocytes and thrombocytes) and hepatic monitoring are required during treatment with Glimeryl. Patients with rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Interactions:** Concomitant administration of Glimeryl with other medicines may result in an undesired increase or decrease in the hypoglycaemic effect of glimepiride. Glimepiride is metabolised by cytochrome P450 2C9 (CYP2C9). The metabolism is known to be affected by concomitant administration of CYP2C9 inducers. Concomitant administration of the following medicines may enhance the hypoglycaemic effect of glimepiride: phenylbutazone, azapropazone and oxyfenbutazone, sulphinpyrazone, insulin and oral antidiabetics, certain long acting sulphonamides, metformin, tetracyclines, salicylates and p - amino- salicylic acid, MAO – inhibitors, anabolic steroids and male sex hormones, quinolones, chloramphenicol, probenecid, coumarin anticoagulants, miconazole, phenfluramine, pentoxifylline (high parenteral doses) fibrates, tritoqualine, ACE inhibitors, fluconazole, fluoxetine, allopurinol, sympatholytics cyclo-, tro- and iphosphamides. The hypoglycaemic effect of glimepiride is reduced thereby resulting in a reduced metabolic control if Glimeryl is administered concurrently with other medicines containing the following active ingredients: oestrogens and progestagens, saluretics, thiazide diuretics, thyroid stimulating agents, glucocorticoids, phenothiazine derivatives, chlorpromazine, adrenaline and sympathicomimetics, nicotinic acid (high doses) and nicotinic acid derivatives, laxatives (long term use), phenytoin, diazoxide, glucagon, barbiturates and rifampicin, acetozolamide. H_2 antagonists, beta-blockers, clonidine and reserpine may either enhance or weaken the blood glucose- lowering effect. During treatment with sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter regulation to hypoglycaemia may be reduced or absent. Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion. Glimepiride may either potentiate or weaken the effects of coumarin derivatives. **Pregnancy and lactation:** Pregnancy: Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. There are no adequate data detailing the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which was probably related to the pharmacologic action (hypoglycaemia) of glimepiride. Consequently, glimepiride should not be used throughout pregnancy. If a patient plans to become pregnant or if a pregnancy is detected during treatment with glimepiride, the treatment should be switched as soon as possible to insulin therapy. Lactation: It is unknown whether the drug is excreted in human milk. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, it is unadvisable to breast-feed during treatment with glimepiride. **Effects on ability to drive and use machines:** The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or as a result of side effects such as visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). **Undesirable effects:** *Uncommon (>1/1.000 and <1/100):* Visual disturbances, Allergic skin reactions such as pruritus, *rash, urticaria. Rare (>1/10.000 and <1/1.000):* Changes in the blood picture, including: moderate to severe thrombocytopenia, leukopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, increased hepatic enzymes. *Very rare (<1/10.000, incl. isolated reports):* Mild hypersensitivity reactions may develop to severe reactions with dyspnoea, fall in blood pressure and possibly shock, allergic vasculitis, cross allergy with sulfunylureas, sulphonamide and related substances, hypoglycaemic reactions, gastrointestinal discomforts such as nausea, vomiting, diarrhoea, epigastric pressure or fullness and abdominal pain, hepatic impairment e.g. with cholestasis and icterus, hepatitis, photosensitivity, drop in serum sodium. **Marketing Authorisation Holder:** Actavis Ltd. B16, Bulebel Industrial Estate Zejtun, ZTN 08 Malta.

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Psychiatric Nursing, the evolving role in mental health

by **Kevin Gafa** *Dip, BSc (Hons)*
Psychiatric Nurse & President MAP-N
Mixed Admission Ward, Mount Carmel Hospital

Psychiatric nursing is an evolving profession which was introduced relatively late in Malta. The roles of psychiatric nurses are diverse and at times difficult to quantify. There has been a need to clearly define these roles for the ever growing number of Maltese psychiatric nurses. This need was fulfilled with the creation of the standards for graduate level psychiatric nurses, which clearly defines the roles and responsibilities of nurses specialised in psychiatry. The Maltese Association of Psychiatric Nurses plays a vital role in creating awareness of the role the psychiatric nurse holds.

Introduction

Psychiatric nursing is a nursing specialty focusing on the fulfilment of the client's needs in mental health in any setting, in partnership with family, significant others and the community.[1]

The roles of the Psychiatric Nurse

Psychiatric nursing is an interpersonal process that promotes and maintains patients' behaviour that results in an integrated functioning of the individual. Stuart and Laraia[2] state that the patient can be an individual, family, group, organisation or the community at large. This obviously implies that the role of the psychiatric nurse is very vast and a clear definition of the role depends on the situation and circumstances the nurse is in. This ranges from a psychiatric emergency in an acute admission ward to a talk given by the psychiatric nurse to the general public on post natal depression. The work of psychiatric nurses is divided into high and low visibility functions. Brown and Fowler[3] identified these functions.

High visibility functions relate to the technical aspects of nursing work, such as giving injections and medications. These functions are valued most by the management as they are tangible and easily related as active nursing skills.

Low visibilities on the other hand, are functions that are associated with building interpersonal relationships, such as warmth and empathy. These skills help to identify and discover the person not the disease.[4] Low visibility functions are most of the time described as non-quantifiable tasks.

Locally, psychiatric nursing can still be considered to be a developing speciality, although the advances in this sector have been significant. The first diploma course specialising in psychiatric nursing started in 1992. Up till then, nurses working at Mount Carmel Hospital were trained in general nursing and had little training in psychiatric care, except for the few who had training in mental health abroad.[5] To date, (March 2007) there are between thirty-five and forty-five psychiatric nurses in Malta. Moreover, the first post-graduate degree in psychiatric nursing started three years ago. Response to this course has been very positive and in December 2006 eleven students successfully completed it while another twenty five are undergoing their studies.

Unfortunately, despite the progress that occurred in recent years, the roles of this speciality are still poorly defined. This could be attributed to the fact that, since mental health care has been operating with virtually no psychiatric nurses for such a long time, some of the responsibilities which are generally attributed to this profession worldwide, were being carried out by various other professionals.

For this reason it was felt that the role of psychiatric nurses should be clearly defined. As a result of this, Mr. Martin Ward, consultant psychiatric nurse and coordinator for mental health courses at the Institute of Health Care (IHC), helped the first group of degree psychiatric nurse to develop standards for graduate level psychiatric nurses in Malta (Table 1). Although these standards are not yet enshrined in the legislation surrounding registration as a psychiatric nurse, they are the excepted expected areas of practice and responsibility. In future, all the education programmes developed for the discipline at IHC will use these as the basis of the competencies for final qualification – in other words the course is designed to enable nurses at the end of their programme to follow these standards satisfactorily and effectively. Standards can serve to foster a sense of unity and identity in the nursing profession.[6] Although standards may vary from one country (or organisation) to another, common standards can be identified; in fact, many of the standards applied in Malta have been adopted from similar standards around Europe, North America and Canada.

Perception of the general public on Psychiatric Nursing

Despite great advances in psychiatric nursing, little research was conducted on the general population's perception of the psychiatric nursing roles. Barker et al[7] performed a pilot study in the form of a face to face survey regarding the role of psychiatric nurses to a convenience sample of 100 passers – by in a shopping area in the centre of Newcastle, England. The pedestrians were asked one simple open ended question, "What do you think a psychiatric nurse does?" The researches found that there is a generally positive perception of the role of the psychiatric nurse, but detected that stigma still surrounds mental illness in general and the professionals working in the mental health field. Almost one third of those interviewed had either no idea what the psychiatric nurse's roles are, or were only able to give vague answers, example, like they look after people in psychiatric hospitals.

continues on page 24

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CONTRA-INDICATIONS
History of hypersensitivity to any component of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria or allergic type reactions after aspirin or NSAIDs including COX-2 inhibitors. Pregnancy and lactation. Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score 10). Estimated creatinine clearance <30 ml/min. Children and adolescents under 16 years of age. Inflammatory bowel disease. Congestive heart failure (NYHA II-IV). Patients with hypertension whose blood pressure has not been adequately controlled. Established ischaemic heart disease and/or cerebrovascular disease.

PRECAUTIONS
Gastro-intestinal effects: Upper GI complications (perforations, ulcers or bleedings), some with fatal outcome have occurred in patients taking etoricoxib. Caution is advised in patients most at risk of developing a GI complication with NSAIDs: elderly, those on any other NSAID or aspirin concomitantly, or those with a prior history of GI disease. There is a further increase in the risk of GI adverse effects (GI ulceration or other GI complications) when etoricoxib is taken together with aspirin (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials. *Cardiovascular:* Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, use for the shortest duration possible and use the lowest effective daily dose. Re-evaluate periodically the patient's need for symptomatic relief and response to therapy, especially in those with osteoarthritis. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with etoricoxib after careful consideration. COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued. *Renal effects:* Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. *Fluid retention, oedema and hypertension:* Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Pay special attention to blood pressure monitoring during treatment with etoricoxib. If blood pressure rises significantly, consider alternative treatment. *Hepatic effects:* Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 60 mg and 90 mg for up to one year. Monitor any patient with symptoms/signs of liver dysfunction or in whom an abnormal liver function test has occurred. Discontinue etoricoxib if signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (3 times the upper limit of normal) are detected. *General:* Take appropriate measures and consider discontinuation, if during treatment, patients deteriorate in any of the organ system functions described above. Maintain appropriate medical supervision when treating the elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with etoricoxib. Serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported associated with the use of NSAIDs including other COX-2 inhibitors and cannot be ruled out for etoricoxib. Discontinue at the first signs of hypersensitivity as hypersensitivity reactions (anaphylaxis, angioedema) have been reported. Etoricoxib may mask fever. Use of etoricoxib is not recommended in women attempting to conceive. 'Arcoxia' tablets contain lactose: do not use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. *Interactions (pharmacodynamic): Oral anticoagulants:* Exercise caution when coadministering with warfarin and other oral anticoagulants. Closely monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose changed in patients receiving oral anticoagulants or similar agents, particularly in the first few days. *Diuretics, ACE-inhibitors and Angiotensin II Antagonists:* NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function, the co-administration of an ACE inhibitor or AIIA and cyclo-oxygenase inhibitors may result in further deterioration of renal function including possible acute renal failure, which is usually reversible. Administer cautiously, especially in the elderly. Patients should be adequately hydrated. Consider monitoring renal function at initiation of therapy and periodically thereafter. *Aspirin:* etoricoxib can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administration of low dose aspirin with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of aspirin **above** those for cardiovascular prophylaxis, or with other NSAIDS is not recommended. *Ciclosporin/tacrolimus:* monitor renal function when etoricoxib and either ciclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic): The effect of etoricoxib on the pharmacokinetics of other drugs: Lithium:* the plasma concentration of lithium is increased by NSAIDS, therefore monitor and adjust blood lithium and lithium dosage if necessary. *Methotrexate.* adequate monitoring is recommended for methotrexate-related toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contraceptives (OC):* Administration of etoricoxib 60 mg with an OC containing 35 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC0-24hr of EE by 37%. Administration of etoricoxib 120 mg with the same OC, concomitantly or separated by 12 hours, increased the steady state AUC0-24hr of EE by 50 to 60%. Consider this increase in EE concentration when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives. *Hormone Replacement Therapy:* 120 mg etoricoxib administered with 0.625 mg Premarin™ (Wyeth) for 28 days increased the mean steady state AUC0-24hr of unconjugated estrone (41%), equilin (76%) and 17-á-estradiol (22%). Although the clinical significance is unknown, take into consideration the increase in estrogenic concentration when selecting HRT as the increase in estrogen exposure might increase the risk of adverse events associated with HRT. *Digoxin:* Patients at high risk of digoxin toxicity should be monitored for an increase in digoxin Cmax when etoricoxib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised by sulfotransferases.* Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. It may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil). *Effect of etoricoxib on drugs metabolised by CYP isoenzymes:* Based on *in vitro* studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test. *Effects of other drugs on the pharmacokinetics of etoricoxib:* The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo. Ketoconazole:* a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC). *Rifampicin:* Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations, an interaction which may result in recurrence of symptoms. *Antacids:* Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent. *Pregnancy:* contraindicated in the first, second and third trimesters of pregnancy. *Lactation:* contraindicated.

SIDE EFFECTS
The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks, or in post-marketing experience:
[Very common (≥1/10) Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000) including isolated cases)] ***Infections and infestations:*** *Uncommon:* gastro-enteritis, upper respiratory infection, urinary tract infection. ***Immune system disorder:*** *Very rare:* hypersensitivity reactions including angioedema anaphylactic/anaphylactoid reactions. ***Metabolism and nutrition disorders:*** *Common:* oedema/fluid retention. *Uncommon:* appetite increase or decrease, weight gain. ***Psychiatric disorders:*** *Uncommon:* anxiety, depression, mental acuity decreased. ***Nervous system disorder:*** *Common:* dizziness, headache. *Uncommon:* dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence. ***Eye disorders:*** *Uncommon:* blurred vision. ***Ear and labyrinth disorders:*** *Uncommon:* tinnitus. ***Cardiac disorders:*** *Uncommon:* congestive heart failure, non-specific ECG changes. *Very rare:* myocardial infarction. ***Vascular disorders:*** *Common:* hypertension. *Uncommon:* flushing. *Very rare:* cerebrovascular accident. ***Respiratory, thoracic and mediastinal disorders:*** *Uncommon:* cough, dyspnoea, epistaxis. ***Gastro-intestinal disorders:*** *Common:* gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea. *Uncommon:* abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting. *Very rare,* peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly). ***Skin and subcutaneous tissue disorders:*** *Uncommon:* ecchymosis, facial oedema, pruritus, rash. *Very rare,* urticaria. ***Musculoskeletal, connective tissue and bone disorders:*** *Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness. ***Renal and urinary disorders:*** *Uncommon:* proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of treatment. ***General disorders and administration site conditions:*** *Common:* asthenia/fatigue, flu-like disease. *Uncommon:* chest pain. ***Investigations:*** *Common:* ALT increased, AST increased. *Uncommon:* blood urea nitrogen increased, creatine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased. The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse effects and severe skin reactions.

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60 and 90 mg Tablets: packs of 28 tablets £22.96. 120 mg Tablets: packs of 7 tablets £6.03 and packs of 28 tablets £24.11 **Marketing Authorisation numbers** Tablet 60 mg PL 0025/0422. Tablet 90 mg PL 0025/0423. Tablet 120 mg PL 0025/0424 **Marketing Authorisation holder** Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK **PDate of review:** June 2005 ® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA. Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

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Letter to the Editor

The Human P

From Professor Albert Cilia-Vincenti MD FRCPath

In a *New Frontiers In Medicine* feature on Human Papilloma Virus (HPV), on page 18 of *The Synapse* Magazine Issue 2/07 of March 2007, a number of questions are given referenced answers. In my view, a few of these answers need clarification.

In answer to "**How does HPV progress to cancer**?", there appears to be a confusion between purely HPV changes ("koilocytosis" in cytology jargon) and CIN (cervical intra-epithelial neoplasia). The world literature is full of confusion between uncomplicated HPV changes and HPV combined with emerging CIN 1 changes. Some authors don't even bother to try and make a distinction between uncomplicated HPV changes and CIN 1, lumping them all under a "low grade lesion" label. This is particularly unsatisfactory in teenage girls where cervical cancer is as rare as hen's teeth, and where slipshod "low grade lesion" reporting may result in unjustified over-investigation and, even worse, over-treatment and damage to young cervices (and possible pregnancy problems).

CIN is a spectrum of precancerous changes, CIN 1 being the mildest. Purely HPV changes are easily over-diagnosed as CIN 1 by cytologists and histopathologists; that is why CIN 1 is said to often resolve spontaneously (because most CIN 1 diagnoses are over-diagnoses of HPV changes). CIN 2/3 changes are far more obvious, and therefore more easily and accurately diagnosed by laboratories; they represent a more advanced stage of precancerous change than CIN 1 and therefore carry higher risk of progression to invasive cancer than CIN 1. This does not mean than genuine CIN 1 is not an early precancerous lesion.

The feature states that CIN 1 (mild dysplasia) includes ano-genital warts. This is incorrect. Ano-genital warts are pure HPV changes. As long as warts have no premalignant changes, they are not CIN 1 nor VIN (vulval intra-epithelial neoplasia).

In answer to "**How is HPV diagnosed**?", the feature states that the Pap test does not screen directly for HPV, and therefore cannot definitely confirm that HPV infection exists or not. This is not

Pharmacists'

From Mr John L. Bonnici B. Pharm

The articles which are published by The Synapse Magazine are very interesting and of excellent quality. Dr Pierre Mallia's contributions have particularly captured my interest, not only from a scientific and ethical point of view, but also on a personal one.

Here in Malta, more so in villages than in the cities, the doctor (although not as much as forty or fifty years ago) still enjoys great respect from patients and there is a particular reason for this. In Malta, doctors (especially in earlier times) were not only people who practising medicine, but were also carrying out duties similar to social workers. They were professionals who were greatly trusted by people.

Furthermore, many doctors took up posts as Presidents of local band clubs and we also have to mention doctors who have excelled in areas which are unrelated to the medical field, such as, literature, archaeology and agriculture (in fact the Maltese Agricultural Society started as 'Societa Medica d'incoraggiamento per il gruppo di Malta' and as far as I remember, the first committee in 1844 had a considerable number of doctors. The inspector of the Agricultural Society in the twenties was Dr Francesco Debono (the highest post which could be achieved within the government in the agricultural sector).

The problem arises when a patient visits a doctor and/or specialist. On many occasions, perhaps because of shyness, the patient does not ask questions to the doctors and more so to the specialists. The patient then presents the prescription to the pharmacist who, believing that the doctor or specialist has explained everything to the patient, dispenses the medicines and turns his/her attention to other clients.

What happens if the patient, for some reason, does not have the required information? The patient can leave the pharmacy and go home as if nothing has happened. Let us presume that he asks the pharmacist, who realises that the medicines can have specific side-effects, example, somnolence or agitation. It is not the first time, that after explaining particular side-effects to patients they ask the pharmacist whether they should indeed take the medication. Who is responsible for the prescription? Does the prescriber have an obligation to explain clearly the side effects to the patient? When doctors or specialists prescribe medicines, they generally ask the patient whether he/she suffers from penicillin allergy and they stop there. Do they have to ask the patient 'Are you allergic to milk?' Why am I asking

Thank you

This issue of The Synapse Magazine marks yet another important milestone for the editorial board and local medical profession alike. The magazine is celebrating its sixth anniversary. Everyone remembers the time when the magazine was being printed as a 4 page black and white leaflet. On the other hand, this issue is being presented as a 28 page full colour magazine. Needless to say, having increased in size does not mean that we have compromised on quality. In fact, the secret to our success is Total Quality Management. Obviously this could never have been accomplished without the sterling contributions of our distinguished colleagues and the steady support of the sponsors. Our collaborators are not merely supporting a magazine which is delivering over 60 articles per year at your doorstep ... they are nurturing a teamwork-based culture driven by continuous medical education.

THANK YOU!

apilloma Virus

entirely correct either. Active HPV changes in smears and biopsies are quite distinctive and easy to diagnose; they are less easy to diagnose with confidence when the HPV infection is subsiding and possibly resolving spontaneously – HPV changes can be over-diagnosed histologically when in fact the viral infection is resolving or has recently resolved.

The feature goes on to state that for women over 30, molecular testing for HPV, in conjunction with Pap test, can identify the viral infection more definitely than Pap test alone. Molecular testing for viral DNA (and also molecular testing for detection of progression from HPV to CIN) is an expensive matter when carried out properly in suitable laboratories. Beware of claims that these PCR (polymerase chain reaction) techniques can be carried out in some small corner of a local private laboratory, to offer cheap and reliable results. The present consensus among dependable workers in this field of cervical cancer prevention, is that these molecular tests are helpful (when carried out in proper facilities) but not indispensable to safely manage patients with HPV changes and with CIN. The smear test and colposcopic biopsy are perfectly adequate tools (in the right cytological and histopathological hands) to diagnose and safely manage women with HPV and CIN changes and to prevent them from progressing to invasive cervical cancer. A recent medical audit of Maltese cervical cancer cases[1] confirmed what has been found elsewhere, namely, that by far the most important reason for disease development was lack of regular smear tests.

References

1. Busuttil R, Dalmas M, Cilia-Vincenti A. *Effectiveness of Opportunistic Screening for Cancer of the Cervix Uteri*. MMJ 2006; 18(3):15-20.

Professor Cilia-Vincenti is Director of Surgical Pathology Services at St Philip's Hospital and a longstanding member of the British Society for Clinical Cytology. He is a former Chairman of Maltese Health Service Pathology, Director of a British Health Care Trust's Pathology Services, and a teacher of London and Malta Universities.

Intervention

this question? Because till now, lactose is used an excipient in medication and people who do not tolerate this carbohydrate, can end up feeling unwell if they take such medication. The same applies to gluten.

I believe that the information pertaining to Non Prescription Drugs or Over The Counter drugs is the responsibility of the pharmacist because these would have been bought without prescription. I also believe that certain basic information about the administration of Prescription Drugs is the responsibility of the pharmacist, example, in the case of tetracyclines which should be taken only with water.

Looking forward to the updates which you send through The Synapse.

Dr Pierre Mallia replies:

First of all I would like to thank Mr. Bonnici for his compliments. He raises two important issues: that of Over T□he Counter Drugs (OTCs) and that of prescriptions given to patients who seem not to have understood or not to have been given enough information. Prima facie the prescription and the giving of information is the doctor's sole responsibility. The pharmacist conversely is responsible for any OTC or drugs 'prescribed' or recommended by paramedics such as podologists (who would usually prescribe creams etc).

The problem arises when the pharmacist detects lack of communication as mentioned. Of course the ethical thing to do is to actually 'be ethical' about it. Many pharmacists liaise continuously with doctors - no one is infallible. If the pharmacist has an objection, it would be prudent to speak to the doctor and make inquiries. Sometimes, for example, a doctor may give a dose which is slightly higher than the recommended dose, purposely. Of course no responsibility can fall on the pharmacist for this. If there are clear-cut errors, the pharmacist always has a right to a moral objection to dispense the said drug. It is always the doctor's duty to take a history. In busy practices mishaps may occur. A doctor may prescribe a drug to a woman in the early stages of pregnancy, not knowing that the woman is pregnant. It is not usual to ask all women whether they are pregnant, and the woman may of course have either just found out or not told the doctor. It is the duty of the pharmacist to point this out, if he or she learns this fact and if the drug is contraindicated. As usual however the essence of teamwork and good clinical practice is good communication between professionals.

Dr Pierre Mallia is Director of the Centre for Bioethics at the Medical School.

Invertebrates in the medical service of man:
Part III – The Research Assistants

by **Charles Savona-Ventura** *MD DScMed FRCOG AccrCOG MRCPI*
Professor of Obstetrics & Gynaecology, Faculty of Medicine & Surgery, University of Malta

The invertebrates have generally been medically classed as disease vectors, though a number of species have been utilized in the management of surgical conditions or for the biotherapeutic properties of their secretions.[1,2] A number of species have been essential tools in frontline research studies which have in some instances received international acclaim.

Phylum Mollusca; Class: Cephalopoda;
Several species of Squids, Cuttlefish and Octopi
Sepioteuthis lessoniana; Sepioteuthis sepioidea; Lolliguncula brevis; Loligo opalescens; Loligo pealei; Illex illecebrosus; Sepia officinalis; Octopus vulgaris

Loligo sp.

In 1909, L.W. Williams noted that the squid possessed a giant nerve cell or more specifically a large projection from the cell which is called an axon. These observations slipped into obscurity until 1936, when the Professor of Anatomy J.Z. Young rediscovered this curiosity. Using a pair of electrodes, Young stimulated surrounding nerve fibers and found that he could only produce large muscle contractions in the mantle when the large vessel-like structure remained intact, confirming that the structure was indeed a single, huge nerve axon. Scientists quickly appreciated the significance of Young's finding in presenting a working neurological model. This enabled scientists to initiate a number of research projects aimed at understanding neural function.

Based on squid models, the British scientists, Alan Hodgkin and Andrew Huxley, in a series of papers published during the 1950s described the behavior of nerve impulses. This sterling work was in 1963 awarded the Nobel Prize. Further researchers working in the field of neural physiology using the squid model were also in subsequent years made Nobel Laureates. These included the American George Wald, honored in 1967 for his research on chemical and physiological processes in the eye, and the British Bernard Katz, honored in 1970 for his discoveries concerning the role played by chemicals in nerve impulses.

Squid research was hampered by the difficulty in breeding these animals in captivity. Several species of squid were experimented with but problems were encountered either because the species was too small or because it generally lived in cold waters. Finally, in 1987 experimentation with the warm-water species *Sepioteuthis lessoniana* yielded promising results and presented researchers with a laboratory-bred animal. The cephalopods have been useful in elucidating physiological information on membrane biophysics, the ion channel, neuron development and injury, cell biology, muscle biomechanics, brain physiology, chemical neural reception, vision and oculomotor functions, equilibrium receptor systems, behavior and neural pharmacology, transmitter functions, melanin synthesis and developmental biology.

Phylum: Arthropoda; Class: Merostomata; Order: Xiphosura
Horseshoe Crab – Limulus poluphemus

Another invertebrate contributor to the understanding of neural processes was the Horseshoe Crab. Much of what we know about the function of our eyes is the result of studies that began over 50 years ago on the large, compound eyes of the horseshoe crab. Its eyes have a relatively simple construction, and the optic nerve is readily accessible. In addition, it is easy to keep *Limulus* alive in the laboratory, making it an ideal animal for eye research. The cornea of *Limulus* eyes was first examined in 1782, while the 19th century was to result in the investigation into the structure of the median eyes (each with a single lens) and the lateral eyes (composed of small hexagonal eyes called *ommatidia*). Physiological studies on the electrical impulses in the horseshoe crab optic nerve were carried out in 1928 by Dr. H. Keffer Hartline, whereas in 1932, electrical responses were recorded for the first time from a single visual receptor of the *Limulus* eye. In 1967, Dr. Hartline was awarded the Nobel Prize for his continuing research on horseshoe crab vision. His researches had elucidated how sensory cells in the retina help the brain process visual cues, enabling horseshoe crabs to see lines, shapes, and borders. This mechanism, called *lateral inhibition,* allows horseshoe crabs to distinguish mates in murky water. Research of this type was helpful for understanding human eye diseases like retinitis pigmentosa, which causes tunnel vision and can lead to total blindness.[3] Other researchers have utilized the horseshoe crab's eyes to identify the visual pigment as rhodopsin (1960), and also related light sensitivity to a circadian clock mechanism in the horseshoe crab's brain that enhances night vision. Building on the Hartline's lateral inhibition and circadian clock mechanism research, the American ophthalmologist Dr. Robert Barlow and his colleagues are investigating the role of vision in potential mate selection. By using dedicated computer models, Dr. Barlow has analyzed how the brain of a horseshoe crab processes signals transmitted from the eyes and optic nerve. It is hoped that in the future, decoding this pathway may provide valuable information for correcting human vision disorders. An extract of the horseshoe crab's blue copper-based blood – lysate – is used to test the purity of a number of medicinal properties. Furthermore certain properties of the shell are used to help speed blood clotting mechanisms and to produce absorbable sutures.

Phylum: Arthropoda; Class: Insecta; Order: Diptera; Family: Drosphilidae
Fruit Fly - Drosophila melanogaster [Maltese – Ferminalle]

Drosophila melanogaster

The fruit fly *Drosophila* has long been a major contributor to our fundamental understanding of genetic processes serving as the primary organism in the development of the chromosome theory of heredity. As with most of the long-established model

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Obesity and Cardiometabolic Risk

by **Stephen Fava** *FACP FEFIM FRCP(Lond)PhD(Exeter)*
Consultant Physician, Diabetologist & Endocrinologist
Head of the Diabetes & Endocrine Unit
St. Luke's Hospital

Obesity is a major risk factor for a number of diseases. It is associated with increased risk of many types of cancer, osteoarthrosis, gall bladder disease, sleep apnoea, falls and injuries and psychological problems. Importantly it is associated with the metabolic syndrome and its component elements, namely hypertension, abnormal glucose tolerance, insulin resistance and dyslipidaemia. These, in turn, increase the risk of cardiovascular disease.

Metabolic Derangements

Adipose tissue releases a number of biologically active molecules that are thought to have a causative role in the pathogenesis of insulin resistance and vascular disease. Serum free fatty acids (FFAs) are generated by lipolysis (breakdown of stored triglycerides). They are increased in obese individuals as a result of increased adipose tissue mass. FFAs induce insulin resistance, possibly by competing with glucose as an energy substrate and by having an inhibitory effect on insulin signaling. The liver takes up FFAs to synthesise triglycerides and packages them with proteins to form very low density lipoprotein (VLDL). FFAs therefore mediate the association between obesity and hepatic steatosis ('fatty liver') and with hypertriglyceridaemia.[1] High serum triglycerides, in turn, result in small dense LDL and low HDL. These lipid abnormalities help explain the association between obesity and cardiovascular disease.

FFAs are also thought to be deleterious to the ß cells of the pancreas (lipotoxicity).[2] They decrease the sensitivity of the pancreas to glucose, so that it secretes less insulin for a given plasma glucose concentration.[3] They also increase apoptosis (programmed cell death) of ß cells, resulting in decreased ß cell mass.[2] The combination of increased insulin resistance and diminished ß cell function predisposes to abnormal glucose tolerance and diabetes.

Other cytokines released by adipose tissue that contribute to increased cardiometabolic risk include tumour necrosis factor alpha (TNFalpha), plasminogen activator inhibitor-1 (PAI-1) and interleukin-6 (Il-6).[4] These molecules decrease insulin sensitivity and are pro-inflammatory. PAI-1 is also pro-thrombotic. Adipose tissue is also an endocrine organ, releasing a number of hormones. These include leptin (see below), resistin (which increases insulin resistance) and adiponectin (which decreases insulin resistance and inflammation).

Metabolic Memory

There is evidence that the metabolic milieu of adipose tissue early in life causes long-term or even permanent changes in their metabolic profile. Undernutrition *in utero* or in early postnatal life, especially if followed by unrestricted access to food later in life, leads to hyperplasia and hypertrophy of adipose tissue and a shift towards release of pro-inflammatory cytokines and insulin resistance.

Visceral vs Subcutaneous Fat

Visceral fat is more strongly associated with cardiometabolic risk than subcutaneous fat. It secretes more FFA, PAI-1 and IL-6. Furthermore, since these molecules are released directly into the portal rather than the systemic circulation, they have a greater effect on the liver, their main site of action.[5] Visceral fat is also more insulin resistant than subcutaneous fat. Furthermore the balance is shifted towards production of resistin rather than adiponectin.

Visceral fat can be measured by CT scan, MRI or other specialized imaging techniques such as dual X-Ray absorptiometry (DXA). However, it is impractical to assess visceral obesity by using these modalities repeatedly in all patients. Fortunately, waist circumference has been found to be a useful indicator of visceral fat. Because it is so easy to measure, it is now used in the definition of 'central obesity' or 'abdominal obesity' in most guidelines.

Control of Food Intake

Obesity is a very difficult condition to treat. It is caused by an interaction of genetic and environmental factors. A key to unraveling both its pathogenesis and its treatment, is an understanding of the physiological control of food intake and hence body weight. This is a very complex subject and only a very brief outline will be given here. The role of the endocannaboid system will be discussed in the next section.

Two centres in the hypothalamus regulate the desire to eat. The feeding centre stimulates eating. The satiety centre inhibits the feeding centre. The activity of the hypothalamic centres is in turn regulated by a number of sensing mechanisms. The hypothalamus can thereby respond to ingestion of a meal (gut hormones), body fat mass (lipostat or adipostat signals) and nutrient status (blood nutrient levels).

A number of gut hormones inhibit food intake in response to food in the gastro-intestinal tract.[6] These include glucagon-like peptide1 (GLP-1), cholecystokinin (CCK), pancreatic polypeptide (PP) and peptide YY. GLP-1 and CCK also stimulate insulin release. Grehlin is a hormone secreted from the stomach in response to starvation and cachecia; it stimulates food intake as well as secretion of growth hormone from the pituitary.

The hypothalamus also receives chemical signals about the body fat mass. Leptin is secreted by adipose tissue in proportion to its mass.[7,8] Leptin acts centrally to inhibit feeding.[9,10] Adiponectin may also serve as an adiposity signal and inhibits feeding. Insulin levels correlate with adipose mass and are increased after meals. Like leptin, insulin's central action is probably to inhibit feeding.

The hypothalamus can also sense directly the levels of certain nutrients in the blood; these include glucose and fats. For example, oleic acid (a constituent of olive oil) inhibits food intake.[11]

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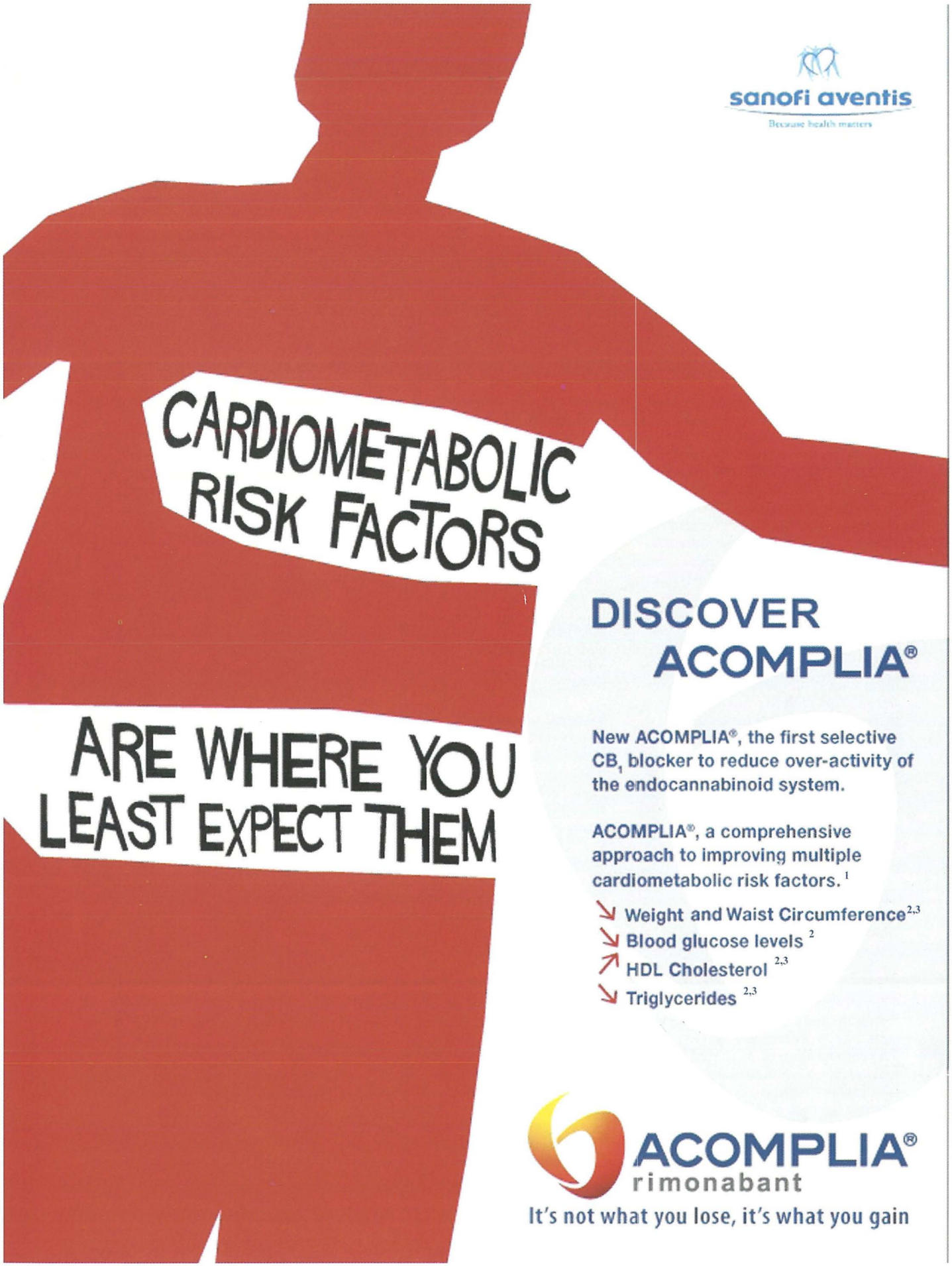

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ACOMPLIA® (rimonabant) Prescribing information Presentation: Biconvex, teardrop-shaped, film coated white tablets containing 20mg rimonabant. Indications: As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30 kg/m2), or overweight patients (BMI >27kg/m2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia. Dosage and Adminstration: 20mg tablet daily to be taken in the morning before breakfast. Treatment should be introduced with a mildly reduced calorie diet. Safety and efficacy of rimonabant have not been evaluated beyond 2 years. See also Precautions and Warnings below. Contraindications: Hypersensitivity to the active substance or to any of the excipients, lactation. Precautions and Warnings: Use with caution in patients over 75 years of age. ACOMPLIA® should be used with caution in patients with moderate hepatic impairment or epilepsy, and is not recommended in patients aged up to 18 years, or patients with severe hepatic impairment or severe renal impairment. Since ACOMPLIA® tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine. Patients should be instructed not to increase their dose of ACOMPLIA®. Depressive disorders have been reported in patients receiving rimonabant. Therapy should not be initiated in patients with uncontrolled serious psychiatric illness such as major depression, until this psychiatric condition is controlled. Use of rimonabant is not recommended in patients taking antidepressant medication. Patients who had had a cardiovascular event less than 6 months ago were excluded in the studies for rimonabant. Interactions: Rimonabant should be used with caution in combination with potent CYP3A4 inhibitors (eg. ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone), which may increase the plasma concentration of rimonabant. CYP3A4 inducers (eg rifampicin, phenytoin, phenobarbital, carbamazepine, St John's Wort) may reduce the plasma concentration of rimonabant and may results in loss of efficacy. Pregnancy and Lactation: Use in pregnancy is not recommended. Patients should notify their physician if they become pregnant during treatment with rimonabant. Use is contraindicated during lactation. Effects on ability to drive and use machines: Rimonabant is devoid of any significant cognitive or sedative effect. Adverse Reactions: Very common – upper respiratory tract infection and nausea. Common – gastroenteritis, anxiety, insomnia, mood alterations, depressive disorders, irritability, parasomnias, nervousness, sleep disorders, dizziness, memory loss, hypoaesthesia, sciatica, hot flush, diarrhoea, vomiting, pruritus, hyperhidrosis, tendonitis, muscle cramp, muscle spasms, influenza, asthenia/fatigue, joint sprain, contusion, fall. Rare – hallucinations. Please consult SPC for full details of the recognised side effects with ACOMPLIA®. Overdose: Experience in overdose is limited. Only minor symptoms have been reported such as headache, euphoria, fatigue and insomnia in single dose tolerability studies. Legal Category: POM. Marketing Authorisation Numbers: EU/1/06/344/002. Marketing Authorisation Holder: sanofi-aventis, 174 Avenue de France, F-75013 Paris, France. Further information is available from: sanofi-aventis Malta Ltd., Triq Kan. K. Pirotta, B'Kara. BKR 1114, MALTA. TEL No. 2149 3022. Ref No: MT_RIM_07_05_04

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1.ACOMPLIA® Summary of Product Characteristics.

2.Scheen AJ et al. Lancet 2006; 368:1660-1672

3.Després J-P et al. N Eng J Med 2005;353:2121–2134

The Human Papilloma virus vaccine

The Do's and Don'ts

by **Christopher Barbara** *MD MSc (Med.Micro.)(Lond.) DLSHTM FMCPath*
Consultant Microbiologist i/c Virology St. Luke's Hospital

The news that a new vaccine, which can prevent a carcinoma, is now available in the market spread throughout the medical field like fire. Of course, the Human Papilloma Virus (HPV) or rather some strains of HPV are implicated in the aetiology of cervical carcinoma.

There are currently two vaccines against HPV in the market – bivalent and a tetravalent vaccine. However, due to cross-immunity these vaccines protect against a proportion of those strains which may lead to cervical carcinoma. Hence, one has to be clear and understand that these vaccines may not fully protect everyone and certainly do not prevent all types of cervical cancer. These strains of the virus are transmitted sexually, so the use of these vaccines should not give a false sense of security and it is very important that regular cervical screening should not be stopped.

The HPV is constituted by a group of over 100 strains of viruses and about 30 of these strains are transmitted sexually and infect the genital area. Most people infected with these viruses are asymptomatic while others may complain of wart like lesions. Of the strains transmitted sexually there are a few which are considered as high risk because they are associated with pre-cancerous changes in the cervix, vulva, anus and penis. Amongst these high risk strains there are HPV types 16 and 18 which cause 70% of cervical cancer and HPV types 6 and 11 which cause 90% of genital warts.

The vaccine should not be given to those who are allergic to ingredients of the vaccine and is not recommended in pregnancy. Otherwise, these vaccines appear to be very safe and may be administered in 3 doses over a period of 6 months. Local inflammation at the site of injection has been observed as well as possible fever, nausea and dizziness.

One has to remember that these vaccines provide immunity to specific strains of HPV but should not be used in the treatment of cervical carcinoma.

The vaccine itself consists of specific protein blocks taken from the virus' outer coat but contains no infectious particles. There is also no thiomersal or mercury in the vaccine. The duration of protection by the vaccine is not yet known but a 5-year protection has been confirmed. Whether a booster dose may be needed later is not yet known.

Since the vaccine protects against the majority of HPV strains transmitted sexually, the vaccine is targeted towards females aged 9 to 26 years as these are sexually active. Studies on women over 26 years are currently being done.

Studies are also being done to discover the degree of protection achieved in males, and the vaccine may be licensed for use in males in the future.

Hence, the HPV vaccine has proved to be a milestone in the advances in medicine as one has achieved protection against carcinoma by vaccination. Although so effective, and free from serious side effects, it is essential to understand that a small proportion of HPV strains are not covered by the vaccine and of course the routine cervical smears for cytological examination as well as the recommendation given to sexually active persons regarding safe sex and/or abstinence is very sound advice.

No teenager must go away with the idea that now that she has been inoculated with the 3 doses of the HPV vaccine, she is safe to practice unprotected sex and runs no risk of HPV infection or cervical carcinoma, not to mention the risk of other sexually transmitted infection like HIV, syphilis, gonorrhea, hepatitis B or herpes infections.

One dream has now come true, and certainly this vaccine will certainly afford protection against one of the common carcinomas in women. The future for vaccination looks very bright.

Update on Avian Influenza

by **Tanya Melillo Fenech** *MD MSc*
Principle Medical Officer at Disease Surveillance Unit, Department of Public Health

The cumulative number of cases is 291 and the deaths are 172 as of Mid April. Since the beginning of the year there have been 28 confirmed human cases (in Indonesia, Nigeria and Egypt) of which 14 have dead. The overall survival rate is 59.4% for human avian patients in Egypt in contrast with the survival rate of 21.7% in Indonesia.The success in Egypt is encouraging and is possibly due to prompt initiations of antiviral tharapy.

The Food and Agriculture Organisation stated that Egypt, Indonesia, and Nigeria have not been able to contain the disease, effectively making them reservoirs of the virus for possible spread to other countries.

The latest on H5N1 virus

The viruses isolated in Thailand from the Phichit province belonged to the genotype Z, whereas the virus isolated from the Nakhon Phanom province belonged to the genotype V. Experts voiced concern over the possibility that the 2 different genotypes, called 'sub-clades', of the H5N1 bird-flu virus found in Thailand could meet and merge into an unknown and 'unpredictable' mutated form.

Latest information on H5N1 Human Vaccine

- The Food and Drug Administration (FDA) stated that clinical trials with 2 doses provided protection to just 45% of male adults who received the highest dose of the Sanofi Aventis avian vaccine. The first vaccine against H5N1 influenza strain to seek FDA approval is thus even less effective than previously thought. However the US is supporting its use as an interim measure until better versions come along, being the only vaccine available right now. Studies have been limited and no data is available on its effect on women, children and those who had the seasonal influenza vaccination. The FDA expressed concern that the immune response among persons who took the Sanofi vaccine was not as strong as its seasonal influenza counterpart.
- The European Medicine Agency has recommended approval of Focetria by Novartis and Daronrix by GlaxoSmithKline as experimental bird flu vaccine for use in humans.

Announcing a new era in vaccination ...

SILGARD®

The one and only quadrivalent vaccine that protects against

CERVICAL CANCER	100%
CERVICAL DYSPLASIA	95%
GENITAL WARTS	99%

caused by Human Papillomavirus Types 6, 11, 16, and 18.

SILGARD® is a vaccine for the prevention of high-grade cervical dysplasia (CIN2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts causally related to Human Papillomavirus (HPV) types 6,11,16,18. The indication is based on the demonstration of efficacy of SILGARD® in adult females 16 to 26 years of age and on demonstration of immunogenicity of SILGARD® in 9- to 15-year o;d children and adolescents.

As with any vaccine, vaccination with SILGARD® may not result in protection in all vaccine recipients. The vaccine is therefore not indicated for treatment of cervical cancer, high-grade cervical, vulval and vaginal dysplastic lesions or genital warts

Now is the time to vaccinate girls and young women 9 to 26 years of age

ABRIDGED PRESCRIBING INFORMATION: SILGARD®(Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)) Refer to Summary of Product Characteristics for full product information. **Presentation:** Silgard is supplied as a single dose pre-filled syringe containing 0.5 ml of suspension. Each dose of the quadrivalent vaccine contains highly purified virus-like particles (VLPs) of the major capsid L1 protein of Human Papillomavirus (HPV). These are type 6 (20 Ìg), type 11 (40 Ìg), type 16 (40 Ìg) and type 18 (20 Ìg). **Indications:** Silgard is a vaccine for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. The indication is based on the demonstration of efficacy of Silgard in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Silgard in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males. The use of Silgard should be in accordance with official recommendations. **Dosage and administration:** The primary vaccination series consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months. If an alternate vaccination schedule is necessary, the second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.The need for a booster dose has not been established. **Paediatric population:** Silgard is not recommended for use in children below 9 years of age due to insufficient data on immunogenicity, safety and efficacy. The vaccine should be administered by intramuscular injection. The preferred site is the deltoid area of the upper arm or in the higher anterolateral area of the thigh.Gilgard must not be injected intravasaularly. Subcutaneous and intradermal administration have not been studied, and therefore are not recommended. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Silgard should not receive further doses of Silgard. Administration of Silgard should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation. **Warnings and precautions:** As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.As with any vaccine, vaccination with Silgard may not result in protection in all vaccine recipients.Also, Silgard will only protect against diseases that are caused by HPV types 6, 11, 16 and 18. Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.Silgard has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, high-grade cervical, vulvar and vaginal dysplastic lesions or genital warts. It is also not intended to prevent progression of other established HPV-related lesions. Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Silgard will not provide protection against non-vaccine HPV types, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations. There are no data on the use of Silgard in subjects with impaired immune responsiveness. Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine.This vaccine should be given with caution to individuals with thrombocytopaenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. The duration of protection is currently unknown. Sustained protective efficacy has been observed for 4.5 years after completion of the 3-dose series. Longer term follow-up studies are ongoing The data on Silgard administered during pregnancy did not indicate any safety signal. However, these data are insufficient to recommend use of Silgard during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy. Silgard can be given to breastfeeding women. **Undesirable effects:** Very common: pyrexia and at the injection site: erythema, pain, swelling. Common: at the injection site: bleeding, pruritus. In addition, in clinical trials adverse reactions that were judged to be vaccine- or placebo-related by the study investigator were observed at frequencies lower than 1%: rare: urticaria and very rare: bronchospasm.
Package quantities: Single pack containing one 0.5 millilitre dose pre-filled syringe with a needle guard and two needles.
Marketing authorisation holder: Merck Sharp & Dohme Ltd, Hertford Road, Haddesdon, Hertfordshire EN11 9BU, United Kingdom.
Marketing authorisation number: EU/1/06/358/015. **Legal category:** POM. **Date of last revision of the text :** September 2006.

Before administering Silgard®, please read the Physician Circular.

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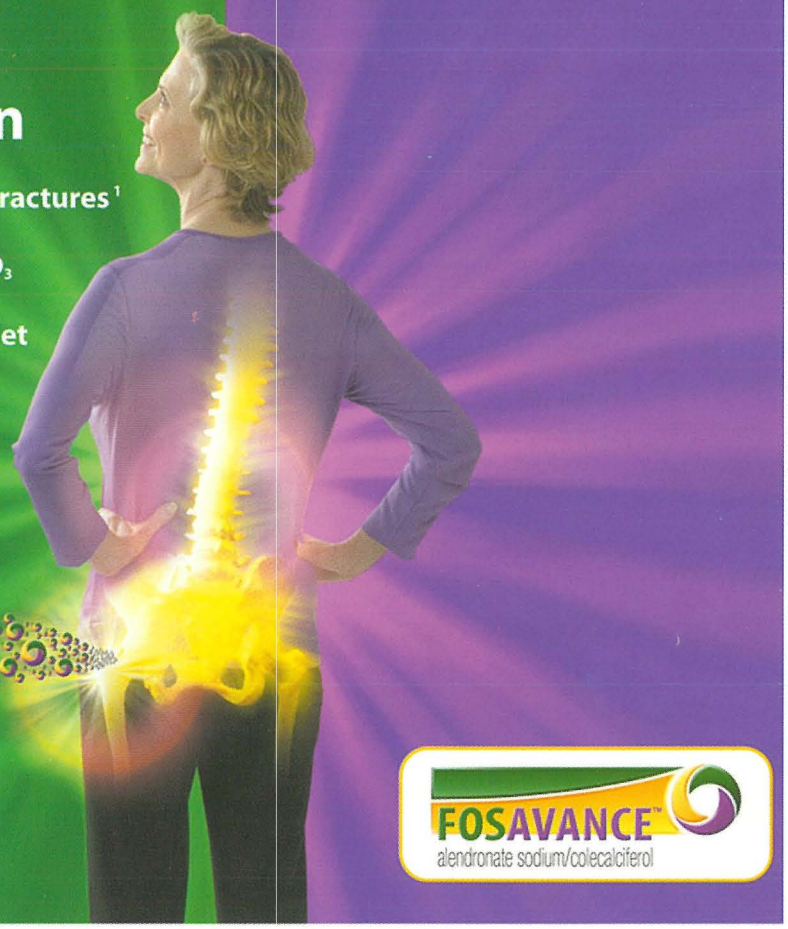
TREATING YOUR POST-MENOPAUSAL OSTEOPOROSIS PATIENTS

FOSAVANCE™ Tablets
(alendronate sodium/colecalciferol)

are a logical progression

- Reduces the risk of hip and vertebral fractures[1]
- Assurance of added vitamin D_3
- One single weekly tablet



FOSAVANCE™
alendronate sodium/colecalciferol

FOSAVANCE™ Tablets (70 mg Alendronic Acid as Alendronate Sodium Trihydrate and 70 micrograms [2,800 IU] Colecalciferol [vitamin D_3])

ABRIDGED PRODUCT INFORMATION
Refer to Summary of Product Characteristics before prescribing.

PRESENTATION
Capsule-shaped, white to off-white tablets marked with an outline of a bone image on one side, and '710' on the other, containing 70 mg alendronic acid as alendronate sodium trihydrate and 70 micrograms (2,800 IU) colecalciferol (vitamin D_3).

USES
Treatment of post-menopausal osteoporosis in patients at risk of vitamin D insufficiency. 'Fosavance' reduces the risk of vertebral and hip fractures.

DOSAGE AND ADMINISTRATION
The recommended dosage is one (70 mg/ 70 microgram) tablet **once weekly**.
Patients must be advised to follow the instructions below:
For adequate absorption of alendronate: Take at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate.
The following instructions should be followed exactly in order to minimise the risk of oesophageal irritation and related reactions:
- Swallow 'Fosavance' only upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Do not chew the tablet or allow the tablet to dissolve in the mouth because of a potential for oropharyngeal ulceration.
- Do not lie down until after the first food of the day which should be at least 30 minutes after taking the tablet.
- Do not lie down for at least 30 minutes after taking 'Fosavance'.
- Do not take at bedtime or before rising for the day.

Patients should receive supplemental calcium if intake is inadequate. Additional supplementation with vitamin D should be considered on an individual basis taking into account vitamin D intake from vitamins and dietary supplements. Equivalence of 2,800 IU of vitamin D_3 weekly in 'Fosavance' to daily dosing of vitamin D 400 IU has not been studied. *Use in the elderly:* No dosage adjustment is necessary. *Use in renal impairment:* No dosage adjustment is necessary for patients where GFR is greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is <35 ml/min. *Use in children.* Not recommended.

CONTRA-INDICATIONS
Oesophageal abnormalities and other factors which delay oesophageal emptying, such as stricture or achalasia. Inability to stand or sit upright for at least 30 minutes. Hypersensitivity to alendronate or to any of the excipients. Hypocalcaemia.

PRECAUTIONS
Alendronate can cause local irritation of the upper gastro-intestinal mucosa and potentially worsen any underlying disease. Use with caution in patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, or ulcers, or with a recent history (within the previous year) of gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty. Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should be alert to any signs or symptoms of a possible oesophageal reaction, and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or new or worsening heartburn. The risk of severe oesophageal adverse reactions appear to be greater in patients who fail to take alendronate properly and/or continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. While no increased risk was observed in extensive clinical trials with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe with complications. A causal relationship cannot be ruled out. Bone, joint and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating. From start of treatment, onset of symptoms varied from one day to several months. A subset had recurrence of symptoms when rechallenged. Patients should be instructed that if they miss a dose of 'Fosavance' , they should take one tablet on the morning after they remember. They should not take two tablets on the same day, but should return to taking one tablet once a week, as originally scheduled on their chosen day. Cause of osteoporosis other than oestrogen deficiency and ageing should be considered. Correct hypocalcaemia before initiating therapy. Other disturbances of mineral metabolism should also be effectively treated. The content of vitamin D in 'Fosavance' is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with 'Fosavance'. *Colecalciferol:* Monitor urine and serum calcium in patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis) as vitamin D_3 may increase the magnitude of hypercalcaemia and or hypercalciuria. Patients with malabsorption may not adequately absorb vitamin D_3. *Excipients:* Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take 'Fosavance' because it contains lactose and sucrose. *Drug interactions* Food, beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products may interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking 'Fosavance' before taking any other medicinal product. *Use in pregnancy and lactation:* alendronate has not been studied in pregnant or breast-feeding women and should not be given to them.

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SIDE EFFECTS
The following adverse experiences have been reported during clinical studies and/or post-marketing use of alendronate. No new adverse reactions have been identified for 'Fosavance'. *Common (≥1.0% and <10%) Gastro-intestinal:* abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distension, acid regurgitation. *Musculoskeletal:* musculoskeletal (bone, muscle or joint) pain. *Neurological:* headache. *Uncommon (≥0.1% and <1%) Gastro-intestinal:* nausea, melaena, vomiting, gastritis, oesophagitis, oesophageal erosions. *Skin:* rash, pruritus, erythema. *Rare (≥0.01% and <0.1%) Body as a whole:* hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute-phase response. Symptomatic hypocalcaemia, often in association with predisposing conditions (see 'Precautions'). *Gastro-intestinal:* oesophageal stricture, oropharyngeal ulceration, upper gastro-intestinal PUBs (perforation, ulcers, bleeding) (see 'Precautions') localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing. *Skin:* rash with photosensitivity. *Special senses:* uveitis, scleritis, episcleritis. Isolated cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. *Laboratory test findings* In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

PACKAGE QUANTITIES AND BASIC NHS COST
'Fosavance' Tablets £22.80 for 4 tablets.

POM Date of review: September 2005

Marketing Authorisation Numbers:
'Fosavance' Tablets EU/1/05/310/02

Marketing Authorisation Holder:
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

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Colorectal cancer

continued from page 2

CT colonography is limited, in that patients must still undergo bowel cleansing. Poor preparation or poor distension will compromise the diagnostic ability of the CT and small and flat polyps are not well detected. Also conventional colonoscopy allows direct biopsy of visualised lesions, while lesions detected with CT colonography require conventional colonoscopic biopsy.

Future developments include stool DNA testing which may be incorporated into colorectal cancer screening algorithms. Colonic neoplasms continuously exfoliate various DNA markers. Targeting multiple DNA mutations found in stool samples may achieve high rates of neoplasm detection with a sensitivity of 91% for cancer and 82% for large adenomas. Mutations on K-*ras*, *APC*, and *p53* genes, as well as mutations on *Bat-26* (a microsatellite instability marker) and long DNA have all been found to be markers for colorectal carcinoma.

The American Cancer Society recommendations for colon cancer screening in average-risk adults 50 years of age and older include:

(a) annual faecal occult blood testing, or
(b) flexible sigmoidoscopy every 5 years, or

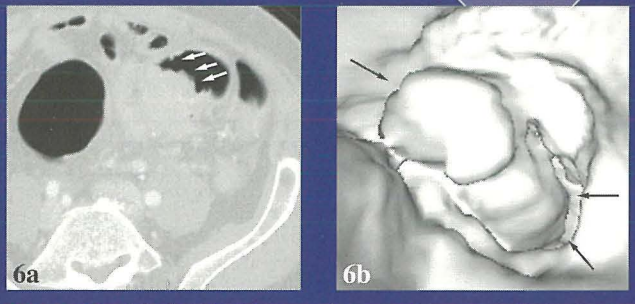

Figure 6. **(a)** *Axial CT scan shows a large carcinoma (arrows) that obliterated the lumen of the sigmoid colon and prevented a complete colonoscopic evaluation.* **(b)** *Three-dimensional endoluminal view shows a large fungating (arrows). The colon proximal to this obstructing mass was easily evaluated with CT colonography.*

(c) annual faecal occult blood testing and flexible sigmoidoscopy every 5 years, or
(d) double-contrast barium enema examination every 5 years, or
(e) colonoscopy every 10 years.

For patients with higher risk, screening is performed according to Table A.

Table A

Risk Category	Age to Begin	Recommendation	Comments
INCREASED RISK			
Previous single, small (< 1 cm) adenomas	Within 3 years	Colonoscopy	If normal, screen as average risk
Previous single large (>1 cm) or multiple adenomas, or high-grade dysplasia or villous change.	Within 3 years	Colonoscopy	If normal, repeat in 5 years; If again normal screen as average risk
Previous curative-intent resection of colorectal cancer	Within 1 year	Colonoscopy	If normal, repeat in 5 years; If again normal, repeat every 5 years
Colorectal cancer or adenomatous polyps, in first-degree relative before age 50, or more first-degree relatives at any age if no hereditary syndrome	Age 40, or 10 years before the youngest case in the immediate family	Colonoscopy	Every 5-10 years. Colorectal cancer in relatives more distant than first-degree does not increase risk substantially above the average risk group.
HIGH RISK			
Family history of familial adenomatous polyposis (FAP)	Puberty	Early surveillance with colonoscopy, and consider genetic testing	If the genetic test is positive, colectomy is indicated*
Family history of hereditary non-polyposis colon cancer (HNPCC)	Age 21	Colonoscopy and consider genetic testing	If the genetic test is positive or if the patient has not had genetic testing, every 1-2 years until age 40, then annually*
Inflammatory bowel disease: Chronic ulcerative colitis, Crohn's disease	8 yrs after onset of pancolitis, or 12yrs after onset of left-sided colitis	Colonoscopy with biopsies for dysplasia	Every 1-2 years*

*These patients are best referred to a centre with experience in the surveillance and management of FAP, HNPCC or IBD.

Dr Pierre Vassallo can be reached at the DaVinci Hospital on 21 491 200 or by email on pvassallo@davincihospital.com.mt

Psychiatric Nursing, the evolving role in mental health

continued from page 12

Table 1: The 15 Standards of Care

1. Collects patient data through pertinent clinical observations based on knowledge of nursing and the behavioural and physical sciences.
2. Involves the individual, family and appropriate others in the assessment, planning, implementation and evaluation of the individual nursing care programme.
3. Uses problem solving techniques in developing a psychiatric/mental health nursing (PMHN) care plan.
4. Promotes the realisation of optimal health (both physical & mental) in individual patients through health teaching.
5. Uses activities of daily living in a goal directed way when interacting with individual patients.
6. Uses knowledge of somatic therapies and related clinical skills whilst working with individual and groups of patients for whom they are clinical responsible.
7. Modifies the environment to establish and maintain a therapeutic milieu.
8. Participates with members of the multi-disciplinary team in assessing, planning and evaluating selected programmes for individual patients.
9. Uses psychotherapeutic interventions to assist the individual patient in achieving optimal mental health.
10. Practices as an accountable health professional in providing psychiatric and mental health nursing.
11. Where appropriate, works with members of the community mental health team to develop and support mental health planning and support for individual patients.
12. Contributes to the leadership of personnel in the provision of PMHN.
13. Assumes responsibility for personnel and professional development and contributes to the professional growth of others.
14. Contributes the development of PMHN.
15. Understands the legal limitations, statutes and acts as a registered graduate PMHN functioning in current mental health care systems within Malta.

Barker et al[7] argued that it is of concern that so many people would not know what to expect from psychiatric nurses, given the number of people with a lifetime chance of developing mental illness and therefore coming into contact with psychiatric nurses. The researchers also divided their findings into negative and positive comments. Negative comments on psychiatric nurses seem to relate to the historical, biomedical model of psychiatric care relating mainly to restraining people and the subordinate role of nurses to medical staff. Positive comments included talking to patients, counselling, caring, supporting, helping, listening, rehabilitating and treating the person as a whole, and were thought to represent a fairly accurate representation of the psychiatric nurse role.[7]

Conclusion

Despite the great advances that have taken place in psychiatric nursing in Malta there is still a long way to go. To this end, a group of psychiatric nurses have set up the Maltese Association of Psychiatric Nurses (MAPN) which aims to act as a point of reference for all nurses working in a mental health setting. The concepts of the association are awareness, education and recognition. MAPN is also helping in the process of defining the important role that psychiatric nurses play in the care of individuals suffering from mental illness and is part of a concrete effort to improve psychiatric nursing as a profession.

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Author can be contacted on e-mail: mapsychnurses@gmail.com. Visit www.map-n.com for more details.

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The A(& E) Team

by **Marika Azzopardi**

Dr Mary Rose Cassar and Dr Anna Spiteri are two female doctors with multiple roles. They are the first two female registrars at the Casualty Department of St Luke's Hospital, practicing what is a relatively new specialization. They are also members of the two year old Malta Resuscitation Council, making headway into an area they feel strongly about.

In a bid to promote resuscitation training in Malta, not only within the medical profession but also for lay people, they are working to see that basic life support is taught as far and wide as possible.

"Basic life support is fundamentally about saving the lives of cardiac arrest sufferers, also with the use of defibrillators. Whilst many people believe this apparatus is only operated in a hospital setting, this is far from true. If we look abroad, defibrillators are placed in public places and may be used by an initial witness of collapse. In the United States, cardiac sufferers are encouraged to possess the apparatus themselves and have a next of kin trained in its operation." Dr Cassar proceeds to comment how once the heart stops, the patient is facing a critical first five minutes that may cost his or her life. Whilst ambulances are at least five minutes away and heavy traffic generally impedes an immediate arrival, those precious five minutes of time are especially valuable.

The Malta Resuscitation Council is specifically concerned about the high rate of cardiac arrests witnessed in emergency departments and the ensuing rate of deaths caused by heart attacks – an estimated one fourth of all deaths are due to cardiac arrest, per year. This substantial statistic indicates an urgent need to give this problem due attention.

Whilst coronary disease is on the increase in Malta, training people in life saving strategies can be extremely cost effective, if only because it could save lives.

"In our work we are finding that high cholesterol levels are increasing the incidence of heart attacks in people who are still in their thirties. We've seen cases where youths as young as 18 years suffer heart attacks. The typical 'dolce vita' of Mediterranean living is being overcome by extremely high levels of stress that is exacerbating the situation."

"People trained in basic life support are extremely valuable. We have so far delivered five 5-hour courses during 2006 in BLS/AED (Basic Life Support/Automated External Defibrillator). We are now planning two more by end of April 2007. The course targets GPs, physiotherapists and lay people. Eventually we aim to go to the Police and Rescue personnel, all of whom recently voiced their interest and requested the delivery of a specific course for their staff." The ultimate aim is to conform to EU standards which indicate that life support trainees and apparatus be present in any location where people may converge.

malta resuscitation council

Dr Spiteri emphasizes that courses are maintained as simple as possible, "This is especially true where they are aimed at lay people. We want to help people retain their skills to be effective life savers. For the moment, our present situation only allows for a two-day course to be delivered once yearly, mainly because of logistic restraints. In fact, we would be facing a considerable problem once we decide to organize more frequent courses.

Another recent accomplishment was the delivery of the EPLS – European Paediatric Life Support – course which stretched for a week and was indicated for staff working with children in a hospital environment.

The two doctors are also proud of the fact that during November 2006, a pilot course was held in Malta which was chosen as an ideal country to host it on a European basis. "The course was very popular and its results were published in international medical journals. It was indicated for doctors working in hospital trauma settings such as emergency doctors, anaesthetists and surgeons. Following the success of the course, which is definitely the most advanced of its genre to be presented ever, it is going to be repeated in other European countries."

Malta is facing a situation which calls for an urgent standardization of the available resuscitation methods in order to ensure the appropriate care for all patients.

Future plans include the organization of further specialized courses being offered to more people, more often. However the biggest hurdle to overcome remains the financial one. Ideally this type of training would be available in Malta, and the council is working towards a scenario which sees Maltese-trained personnel delivering courses on a nation-wide basis. "In some cases we had to bring in 10 externals to run one particular course, and that makes for extremely high costs. We do receive the occasional sponsorship by government to cover part of the costs, but it is not always enough. This means that many local doctors still have to shoulder high expenses to travel abroad and be trained elsewhere. Ideally it would all be available here – widening the life-saving potential on our Islands, reducing financial burdens to the cardiac department and eventually, why not, exporting the training and skills elsewhere."

For further information on the Malta Resuscitation Council check out www.resus.org.mt or call 25954033/25952096.

Obesity and Cardiometabolic Risk

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The endocanniboid system (ECS)

It has long been known that the plant *cannabis sativa* stimulated appetite and had a number of metabolic effects. These effects are receptor-mediated. This had long raised the suspicion that there must be endogenous cannabinoids. These have indeed now been identified and characterized. The endogenous cannabinoids are arachnidonic acid derivatives produced by cell membranes. They act locally and are rapidly inactivated. Their receptors are expressed in many tissues including the hypothalamus, adipose tissue, liver and skeletal muscle. Overactivity of the ECS results in hyperphagia, fat accumulation, decreased glucose uptake by skeletal muscle, increased lipogenesis in the liver and adipose tissue, decreased adiponectin production and insulin resistance.[12]

The ECS therefore presents a novel and exciting target for pharmacological intervention, since its blockade may not only be useful in the treatment of obesity but also directly improves many of the metabolic derangements that contribute to the cardiovascular risk associated with it. Indeed the Rimonabant in Overweight/Obese (RIO) trials have shown very promising and exciting results.[13-16] Blockade of the ECS by rimonabant, reduced weight and waist circumference (central obesity), and improved blood pressure, blood glucose, triglycerides, insulin sensitivity, small dense LDL and HDL. In diabetic patients there was a lowering in HbA_{1c}. Furthermore, many of these metabolic effects occurred independently of its effect on obesity and are therefore attributable to a direct effect over and above that associated with a reduction in obesity. These included a decrease in triglycerides, fasting insulin, HBA_{1c} and a rise in HDL.

Conclusion

Obesity should be regarded as a disease since it is associated with significant mortality and morbidity. Much of this is due to an increased risk of vascular disease as a result of various metabolic derangements. Obesity should therefore be treated aggressively. Unfortunately, treatment has proved difficult. Blockade of the ECS offers another exciting new tool on our armamentarium that targets not only obesity but also its associated cardiometabolic risk.

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Invertebrates in the medical service of man:
Part III – The Research Assistants

organisms, the initial choice for using this species was for practical reasons. The fruit fly is small and has a simple diet and hence large numbers of flies can be maintained inexpensively in the laboratory. The life cycle is also very short, taking about two weeks, so large-scale crosses can be set up and followed through several generations in a matter of months. Fruit flies also have large polytene chromosomes, whose barcode patterns of light and dark bands allow genes to be mapped accurately.

In the early 1900s, American-based geneticists began to make important contributions to genetic research. Working at Columbia University in 1910, Thomas Hunt Morgan conducted experiments in fruit flies, mainly *Drosophila melanogaster*, and established that some genetically-determined traits were sex-linked. Morgan's work was followed up by his students – Calvin Bridges in 1913 established that genes were located on chromosomes; while Alfred Sturtevant in 1913 determined that the genes were arranged on the chromosomes in a linear fashion and further demonstrated that the gene for any specific trait was in a fixed location or locus. Yet another of Morgan's students, Herman J. Muller, in 1926 discovered methods for artificially producing mutants in fruit flies by ionizing radiation and other mutagens, thus discovering the origin of new genes by mutations. These studies opened a new vista for understanding the principles of genetics, mutations and chromosome behavior. A second major contribution of *Drosophila* research has been in our understanding of development. The development of a single egg cell into a many-celled organism is a complex process. The system of patterning genes and signaling molecules in the fruit fly leads to the direct development of different organs in their proper locations. In 1980, Christiane Nusselein-Volhard and Eric Wieschaus performed the first genome-wide mutational screen in an attempt to identify all genes involved in development. In acknowledgement for the work on Drosophila developmental genetics, Ed Lewis, Christiane Nusslein-Volhard and Eric Wieschaus were awarded the Nobel Prize for medicine and physiology in 1995.[4]

The fly genome was sequenced in the year 2001 by J. Craig Venter and the Celera corporation, although much of the work had already been laid by the Berkelely, European, and Canadian *Drosophila* genome projects. The genome is made up of 165 million base pairs in length (spread over four chromosomes) and contains approximately 14,000 genes. The full sequence of the *Drosophila* genome adds to the usefulness of the fly as a model organism. Now that the *Drosophila* genome has been sequenced, the genetic code will greatly facilitate positional cloning methods. The new sequence has also revealed previously unknown counterparts to human diseases, most notably cancer and neurological diseases. With this new knowledge, it is possible to model human diseases and disease pathways in flies. Additionally, it is now possible to systematically study entire networks of genes at once, rather than individual pathways. Consequently, studies in fruit flies will reveal important insights into human physiology and medicine. Finally, the fruit fly could be the key to answering the great question of how a genome can give rise to an organism without any instructions for doing so, possibly serving as the key for artificial organ production from stem cells.

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