Issue 04/09

NEWSPAPER POST

TheSynapse

The Medical Professionals' Network

MEDICAL IMAGING

# Breast Masses in Children - Part I

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*Discovery of breast masses in children and adolescents often causes tremendous parental and physician concern because of the high prevalence of breast cancer in the adult population. However, the prevalence of breast cancer in this age group is low, and knowledge of the spectrum of pathologic conditions and radiological findings that affect the pediatric breast is important in guiding management.*

Breast lesions in children and adolescents are managed differently from those in adults. Unlike in adults, the initial breast imaging study performed in pediatric patients is ultrasound, whereas mammography is reserved for selected cases. Advantages of ultrasound over mammography include lack of ionizing radiation in a susceptible population and greater sensitivity in the relatively dense fibroglandular tissue of young girls. Mammography has a role in the evaluation of microcalcifications and of suspicious discrete masses in older adolescents. Also biopsy and surgical intervention are more cautiously employed in children and adolescents due the low prevalence of breast cancer in this age group and the risk of injuring the developing breast.

The onset of breast development is called Telarche and occurs in white girls at 7-8 years of age and about a year earlier in the black population. At telarche breast development may be asymmetrical, which may cause concern. However ultrasound can confirm normal glandular development and exclude a lesion. It is important to recognise the stages of breast development (Tanner stages 1-5, Figure 1) that are visible on ultrasound examination between the ages of 7 and 13 years, whereby initially the ductal system is develops followed by the fibroglandular tissue and subcutaneous fat.

Premature thelarche may occur as an isolated event or as part of precocious puberty. Isolated premature thelarche generally occurs in girls aged 1–3 years and is nonprogressive. Reassurance is all that is required. However, if the patient has clinical evidence of other forms of sexual maturation, such as axillary and

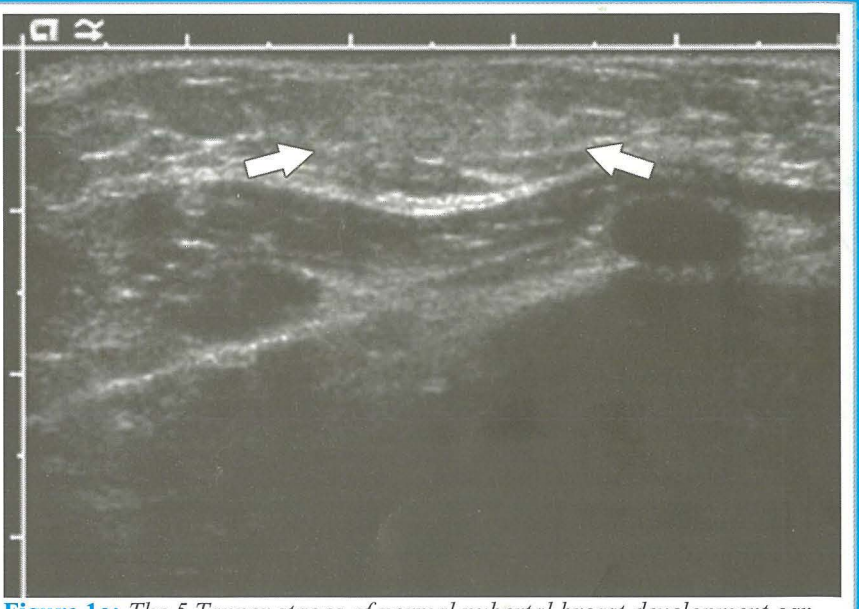

**Figure 1a:** *The 5 Tanner stages of normal pubertal breast development can be recognised on ultrasound. Tanner stage 1 appears as a small area of ill-defined echogenic tissue in the retroareolar region (arrows).*

groin hair growth or vaginal bleeding, a work-up for precocious puberty should be pursued. Radiologic evaluation for suspected precocious puberty should include a bone age assessment and abdominal and pelvic ultrasound to look for evidence of maturation of the uterus and ovaries. In addition, the ovaries and adrenal glands should be evaluated for oestrogen-producing lesions, including functioning ovarian cysts, juvenile granulosa cell tumors of the ovary, and rare feminizing adrenal cortical tumors.

Excessive development of the male breast is called gynaecomastia and clinically manifests as tender, firm subareolar nodules. In children, gynaecomastia often occurs during the neonatal period and puberty. Bilateral enlargement of the breasts is common in neonates because of the influence of maternal hormones. At puberty, two-thirds to three-fourths of boys have some degree of breast enlargement, which peaks at age 13–14 years and usually resolves within 2 years. The condition is usually bilateral but may be unilateral, and it may be familial. The aetiology of gynaecomastia is thought to be a decrease in the ratio of testosterone to oestrogen. Excessive body fat may lead to increased conversion of testosterone to oestrogen.

*continues on page 18*

## Editor's Word

# Of glowing transgenic marmosets & shikimic acid

Today it seems that we are experiencing changes at a much faster rate. Remember the last editorial highlighting the fact that the WHO had raised the level of influenza pandemic alert to phase 5, a step away from a global pandemic? Well, today, a few weeks down the line, not only we have witnessed the WHO announce a pandemic, but Malta has jumped from a zero-case scenario to almost 300 H1N1 cases. The pandemic is spreading like a drop of ink on blotting paper, notwithstanding the fact that countries have gone to extremes such as airport thermal scanners to detect H1N1 cases at their borders.

This is in turn leading to both challenges and initiatives. Apart from the concerns of counterfeit antivirals, pharmaceutical companies and governments now also have to face other limitations, including prices of excipients. Skyrocketing prices of shikimic acid, a key ingredient in the manufacture of oseltamivir, could hinder cost-effective supplies of the drug. In fact its price has risen 900% over the past few months. Amidst all this, the first cases of viral resistance to oseltamivir also started to appear. However, on a more positive note, last July we have seen the first human trials beginning in Australia by the Biotech firm CSL. Also, we have seen Sanofi-Aventis pledging 100 million doses of influenza vaccine to the WHO to help developing countries face the pandemic. Such social responsibility is commendable.

In order to tackle the challenges which are currently presenting themselves, we are also seeing the UK embark on a number of initiatives. The medicines regulator, MHRA, has launched a new webpage specifically for reporting adverse drug reactions associated with the oseltamivir and zanamivir - hopefully we will see this pharmacovigilance tool being implemented by other countries as well. Furthermore, the UK has recently opened a Genome Analysis Centre in Norwich. It is hoped that the genomic analysis of microbes will help the country develop new antibiotics to fight superbugs. Besides, plans to create an innovation investment fund have been announced. The targeted £1 billion over the next 10 years will be used to invest in technology-based businesses with high growth potential. Such initiatives will most certainly place the UK at a competitive edge with regards to R&D in Europe.

Finally, an article published in *Nature* recently reported that researchers in Japan have succeeded in creating the first transgenic primate, a marmoset, one of which has passed on its modified genetic traits to its offspring. Though primates that make a glowing protein have been created before, these are the first to keep the change in their bloodlines. The research team has introduced a gene into marmoset embryos that allows them to build a green fluorescent protein (GFP) in their tissues. GFP was originally isolated from the jellyfish *Aequorea victoria*, which glows green when exposed to blue light. The breakthrough could eventually lead to animal models of disease which mimic much more closely the human genetic and physiological make-up.

Ian Ellul

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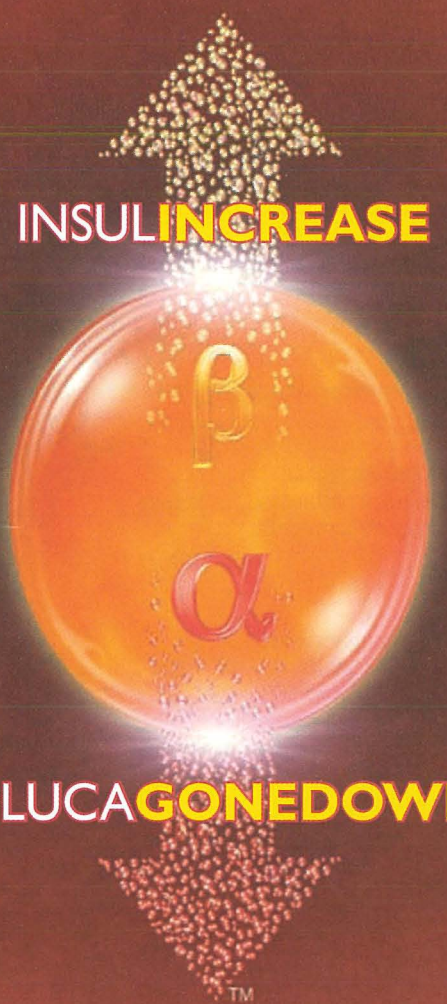


**GALVUS** is a DPP-4 inhibitor that improves glycemic control through powerful islet enhancement[1]

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**Eucreas®**

**Presentations: Eucreas 50 mg/ 850 mg film-coated tablet. Eucreas 50 mg/1000 mg film-coated tablet.** Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **Indications:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. **Dosage and Administration:** The recommended daily dose should be based on the patient's current regimen of vildagliptin and /or metformin hydrochloride. The usual dose is 50 mg/850 mg or 50 mg/1000 mg twice daily one tablet in the morning and the other in the evening. Eucreas should be taken with or just after food. Doses of vildagliptin greater than 100 mg are not recommended. Patients > 65 taking Eucreas should have their renal function monitored regularly, Eucreas is not recommended in patients >75 years. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. **Contraindications:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock. Hepatic impairment. Acute alcohol intoxication, alcoholism, Lactation **Precautions/Warnings:** Eucreas should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Vildagliptin should be used with caution in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II and is not recommended in patients with NYHA functional class III-IV. Metformin is contraindicated in patients with heart failure, therefore Eucreas is contraindicated in this population. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. **Pregnancy and lactation:** Eucreas should not be administered during pregnancy or lactation. **Interactions:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **Adverse reactions:** Rare cases (>1/10,000 to <1/1,000) angiodema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin Monotherapy: Common (>1/100, <1/10): dizziness, Uncommon (>1/1,000, <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10) Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination vildagliptin with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. **PACK SIZES:** 30, 60 film-coated tablets **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002–3, EU/1/07/425/8-9. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. Consult full Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma, P.O. Box 124, Valletta VLT 1000, Malta. Tel +356 22983217 2009-MT-01 EUC Feb 09

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Galvus vildagliptin

1. Novartis Europharm Ltd. Galvus® Summary of Product Characteristics 2009
2. Novartis Europharm Ltd. Eucreas® Summary of Product Characteristics 2009

Eucreas vildagliptin/metformin

# Targeting chemokines: new drugs for old diseases

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*Chemokine receptor antagonists are set to become novel important pharmacological tools within the current therapeutic repertoire available for the management of various inflammatory conditions.*

Currently in various phases of drug development, these molecules act by inhibiting specific inflammatory pathways, and current research suggests a safer adverse effect profile for these drugs than today's therapy.[1]

## Introduction

Chemokines represent a large family of proteins that are produced by a variety of cells, including stromal cells, epithelial cells and immune cells. They are cell activators and chemoattractants, regulating the traffic of cells through a chemotactic gradient. They have a pivotal role in the trafficking of a variety of leukocytes such as T-lymphocytes and neutrophils and endothelial cells: (a) within primary lymphoid organs, (b) from primary to secondary lymphoid organs, (c) between secondary lymphoid organs, and (d) during a humoral immune response.[2] They therefore posses an essential role in both the inflammatory and immunological processes.

## Classification

Over forty human chemokines have been currently identified (Table 1), and these have been classified by structure into four sub-classes, according to the number and spacing of conserved cysteine residues in the chemotactic domain. These four sub-classes are given the preferred names C, CC, CXC and CXXXC, with CC possessing two cysteine residues adjacent to each other, CXC and CXXXC possessing one and three amino acids respectively between the cysteine residues and the C having one of the two cysteine residues missing (Figure 1)

| Chemokine | Former designation | Receptor(s) |
|---|---|---|
| CCL3 | MIP-1α | CCR1, CCR5 |
| CCL5 | RANTES | CCR1, CCR3, CCR5 |
| CCL8 | MCP-2 | CCR1, CCR2, CCR3 |
| CCL17 | TARC | CCR4 |
| CXCL12 | SDF-1, PBSF | CXCR4 |

**Table 1:** *Some chemokine ligands and their specific receptors*

*MIP-1α : Macrophage inflammatory protein 1 alpha, RANTES: Regulated upon Activation, Normal T-cell Expressed, and Secreted, MCP-2: Macrophage chemoattractant protein 2, TARC: Thymus and activation-regulated chemokine, SDF-1: stromal cell-derived factor-1, PBSF: pre-B cell growth-stimulating factor.*

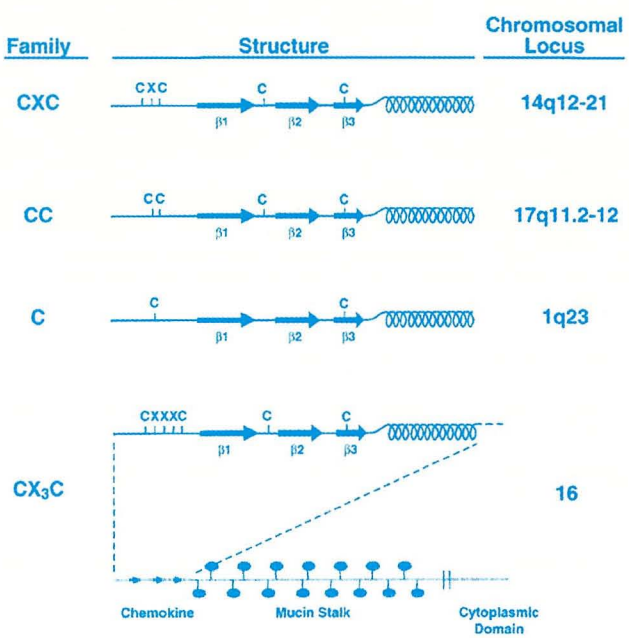


**Figure 1:** *The common structure and chromosomal location of the four chemokine sub-classes, showing the location of cysteine residues, after which they are named. All chemokines have at least three β-pleated sheets (indicated as β1-3) and a C-terminal α-helix. The CX3C chemokine domain occurs at the end of a long stalk which is heavily substituted with mucin-like carbohydrates. The protein is embedded in the membrane and has a short cytoplasmic domain. (Reproduced from Rollins, 1997.[22])*

## Chemokine receptors

Chemokine receptors are structurally and functionally related proteins, that are members of the class A G-protein coupled receptors (GPCRs); they are all coupled to $G_{inhibitory}$ proteins.[3]

Currently 18 proteins that meet the definition for a chemokine receptor exist, with each sub-family of the chemokine class of inflammatory mediators having its own sub-class of receptors. Of these 18 known proteins, 10 are known to be CCRs, 6 are CXCRs, and only one receptor is known for each of the CXXXC and C sub-classes (CXXXCR1 and XCR1 respectively).

Of all of these receptors, it is of interest to note that only the CXCR4 has been found to be essential for life.[4]

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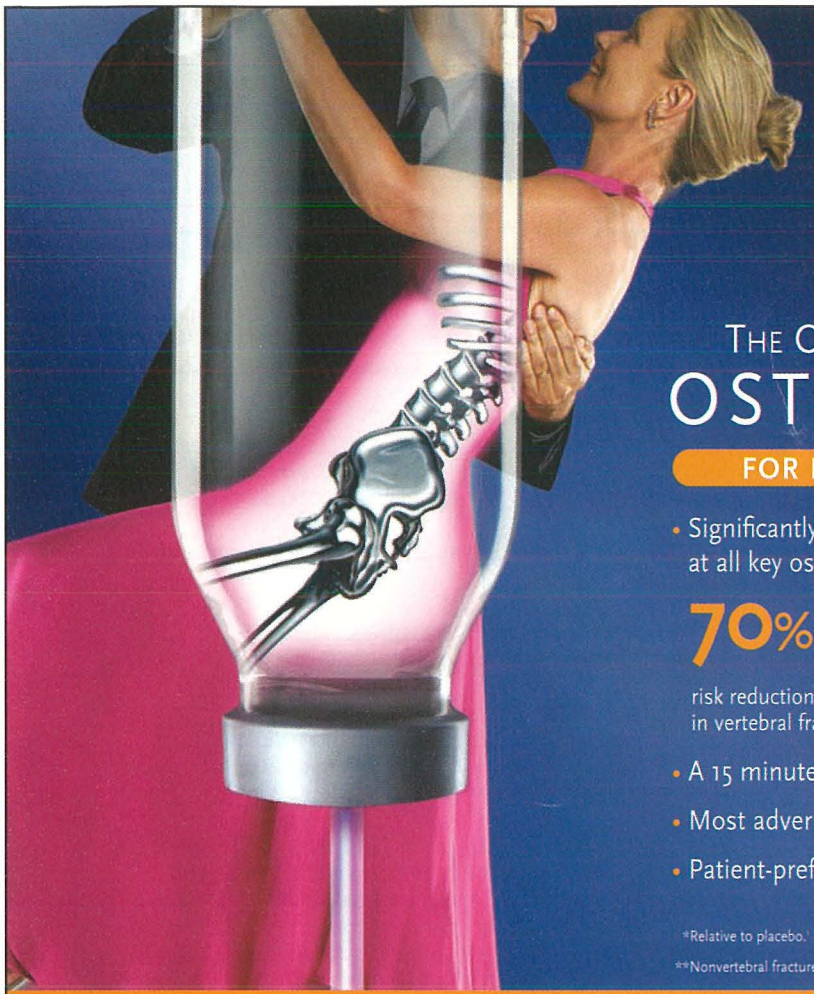

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**70%** risk reduction in vertebral fracture[1]

**41%** risk reduction in hip fracture[1]

**25%** risk reduction in nonvertebral fracture[1]**

- A 15 minute, once-yearly infusion ensures yearlong compliance[1]
- Most adverse events were transient and mild to moderate[1,2]
- Patient-preferred over weekly oral alendronate[3,4]

*Relative to placebo.[1]

**Nonvertebral fracture includes wrist, rib, arm, shoulder, or hip fracture; excludes finger, toe, or craniofacial fracture.[1]

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**PRESENTATION:** Zoledronic acid. 100 mL solution bottle contains 5 mg zoledronic acid (anhydrous), corresponding to 5.330 mg zoledronic acid monohydrate.

**INDICATIONS:** Treatment of osteoporosis in post-menopausal women and men at increased risk of fracture, including those with a recent low-trauma hip fracture. Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture. Treatment of Paget's disease of the bone.

**DOSAGE AND ADMINISTRATION:** Osteoporosis: A single intravenous infusion of 5 mg Aclasta administered once a year. In patients with a recent low-trauma hip fracture, it is recommended to give the Aclasta infusion two or more weeks after hip fracture repair. Paget's Disease: A single intravenous infusion of 5 mg Aclasta. Specific re-treatment data are not available for Paget's disease. Aclasta is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes. Patients must be appropriately hydrated prior to administration of Aclasta, especially important for the elderly and for patients receiving diuretic therapy. Adequate calcium and vitamin D are recommended in association with Aclasta administration. In patients with recent low-trauma hip fracture a loading dose of 50,000 to 125,000 IU of Vitamin D is recommended prior to the first Aclasta infusion. Not recommended for use in patients with severe renal impairment (creatinine clearance <35 ml/min). No dose adjustment in patients with creatinine clearance ≥35 mL/min, or in patients with hepatic impairment, or in elderly patients. Aclasta should not be given to children or adolescents.

**CONTRAINDICATIONS:** Hypersensitivity to zoledronic acid or to any of the excipients or to any bisphosphonate; hypocalcaemia; pregnancy; lactation.

**PRECAUTIONS AND WARNINGS:** Serum creatinine should be measured before giving Aclasta. Not recommended in patients with creatinine clearance <35 ml/min. Appropriate hydration prior to treatment, especially in the elderly and in combination with diuretics. Use with caution in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration); pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly advised that patients with Paget's disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget's disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. A patient being treated with Zometa should not be treated with Aclasta. As a precaution against osteonecrosis of the jaw (ONJ) a dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Aclasta is not recommended in women of childbearing potential.

**INTERACTIONS:** Specific drug-drug interaction studies have not been conducted with zoledronic acid. Caution is recommended when Aclasta is used concomitantly with drugs that can significantly impact renal function, such as aminoglycosides and diuretics that can cause dehydration.

**ADVERSE REACTIONS:** The incidence of post-dose symptoms (e.g. fever, myalgia, flu-like symptoms, arthralgia and headache) are greatest with the first infusion and decrease markedly with subsequent infusions. The majority of these symptoms occur within the first three days and were mild to moderate and resolved within three days of the event onset. The incidence of post-dose symptoms can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration. Very common: Fever. Common: Flu-like symptoms, chills, fatigue, pain, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, pain in extremity, vomiting, nausea, headache, dizziness, atrial fibrillation, hypocalcaemia†, rigors†, ocular hyperaemia, atrial fibrillation, diarrhea, increased C-reactive protein. Local reactions: redness, swelling and/or pain. Others: renal dysfunction and osteonecrosis of the jaw. † Common in Paget's disease only. Please refer to SmPC for a full list of adverse events.

**PACK SIZE:** Aclasta is supplied in packs containing one 100ml bottle

**LEGAL CATEGORY:** POM.

**MARKETING AUTHORISATION NUMBER:** EU/1/05/308/001.

**MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

Consult full Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma, P.O. Box 124, Valletta VLT 1000, Malta. Tel +356 22983217. (vsn 2009-MT-001)

**References:** **1.** Aclasta SmPC. Novartis Europharm Ltd. **2.** Black Dm, Delmas PD, Eastell R, et al; for the HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007; 356:1809-1822. **3.** Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone. 2007; 40:1238-1243. **4.** McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone. 2007;41:122-128.

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# Update on H1N1 Virus

*by* **Tanya Melillo Fenech** *MD MSc*
*Resident Specialist*
*Head, Infectious Disease Prevention and Control Unit*
*Department of Health Promotion and Disease Prevention*

## Global situation

Up to the 2nd of August, in Europe there have been confirmed 26,513 confirmed cases with 40 deaths. Globally there are 158,357 confirmed cases with 1,212 deaths. However the actual number of persons worldwide who have contracted H1N1 virus is likely to be ten times what has been confirmed.

## Local situation

The first two cases confirmed to be positive to H1N1 virus in Malta occurred on 1st July. During that week the initial response was to contain the number of infected cases. The confirmed cases were isolated for 7 days from onset of illness and given antiviral treatment whilst their close contacts were identified and put in voluntary quarantine for 7 days and given prophylaxis with antivirals for 10 days. Within a week there were 48 confirmed cases positive to Influenza A, H1N1 and 14 confirmed cases positive to Influenza A. The majority of confirmed cases were imported cases due to travel to Spain, UK and Cyprus. The first locally transmitted cases occurred in Gharb, Gozo. From the first 62 cases, 81% reported fever while 68% had sore throat and 65% a dry cough.

*... the actual number of persons worldwide who have contracted H1N1 virus is likely to be **ten times** what has been confirmed*

On 8th July the National Pandemic Committee of Health decided to switch from containment phase to mitigation phase and it was decided that only those persons who were at high risk of developing complications from influenza would be swabbed if they develop influenza-like illness and those that come positive will be treated with antivirals. Tracing of close contacts stopped. The 3 groups considered at high risk were:

1) children under 5 years of age;
2) pregnant women;
3) those suffering from the following chronic diseases (chronic respiratory and heart disease, diabetes, immunosuppression and chronic renal failure).

Up to end of week 32 there were 497 negatives, 101 influenza A positives and 222 Influenza A H1N1 positives. Since mitigation started, we have had 9.7 % of our high risk groups positive to Influenza A and 20.4% positive to Influenza A H1N1.

Sentinel surveillance on influenza-like symptoms started to be collected from 15th July both epidemiologically and virologically (doctors are encouraged to participate - please visit http://www.thesynapse.net/articles/viewarticle.asp?artid=11094). Out of 58 sentinel patients swabbed, 25 (43%) were found to be positive to Influenza A H1N1, 8 (14%) positive to Influenza A and 25 (43%) were negative. During week 30 the rate of influenza-like illness was 110.67/1000 consultations.

## Adverse effects of Antivirals

Like all medication, antivirals have side effects. Two studies were done by the Health Protection Agency in the UK at the beginning of the epidemic. A study done on 103 children at three London schools showed that 53% suffered side effects.

The most common were nausea (29%), stomach pain or cramps (20%) and problems related to sleeping (12%). Another study done on a secondary school found that 51% of pupils had symptoms of nausea (31%), headaches (24%) and stomach ache (21%).

All side effects caused by antivirals should be reported to the Medicines Authority.

### H1N1v influenza in pregnant women

The CDC (Communicable disease Centre in the US) collected data from pregnant women infected with influenza A H1N1 virus and concluded that they are at an increased risk for complications from the virus, with a higher estimated rate of hospital admissions than in the general population. Information about the safety and effectiveness of antivirals during pregnancy is scarce.

The European Medicines Agency (EMEA) CHMP assessment report (29/5/09) stated that based on experimental animal studies, Oseltamivir therapy during pregnancy is not expected to increase the risk of congenital anomalies. Overall from the data collected there does not appear to be evidence to suggest that maternal exposure to oseltamivir was associated with adverse pregnancy or foetal outcome.

The conclusion was that overall, the benefit of using Oseltamivir in pregnant or breast-feeding women outweighs the risk to the foetus in the context of a novel influenza H1N1 pandemic situation.
shown that Zanamivir crosses the placenta and is secreted in breast milk. However taking the overall data, it is suggested that the benefit in pregnant and breast-feeding women outweighs the risk in a pandemic situation.

## H1N1 influenza in children under 1 year of age

The CHMP report (29/5/09) states that it acknowledges that there is limited data available supporting the use of Oseltamivir in children below 1 year of age. However considering the urgent need for recommendations to treat this population since an H1N1 pandemic situation has been declared and these children are at high risk of developing complications of influenza, the appropriate dosage for treatment for children below 1 year of age is 2-3mg/kg twice daily for 5 days. Children below 3 months of age should be treated under medical supervision in hospital.

## Pandemic vaccine

A press release by EMEA (24/7/09) states that they are reviewing data on H1N1 vaccines. 4 mock up vaccines developed by Baxter, GlaxoSmithKline and Novartis have already been approved in the EU based on earlier data generated with the H5N1 virus strain. These vaccines were developed with the knowledge that the virus strain would be changed in the event of a declared pandemic to include the strain causing the pandemic. Clinical trials have initiated on efficacy, immunogenicity and safety of the vaccine and initial results are expected from September 2009. As with all medicines, rare adverse reactions can only be detected during the wider use of the vaccine. Besides the mock up vaccines, a number of pandemic vaccines are currently under development and preliminary data from GSK and Sanofi Pasteur are also being assessed by the Committee on an accelerated basis.

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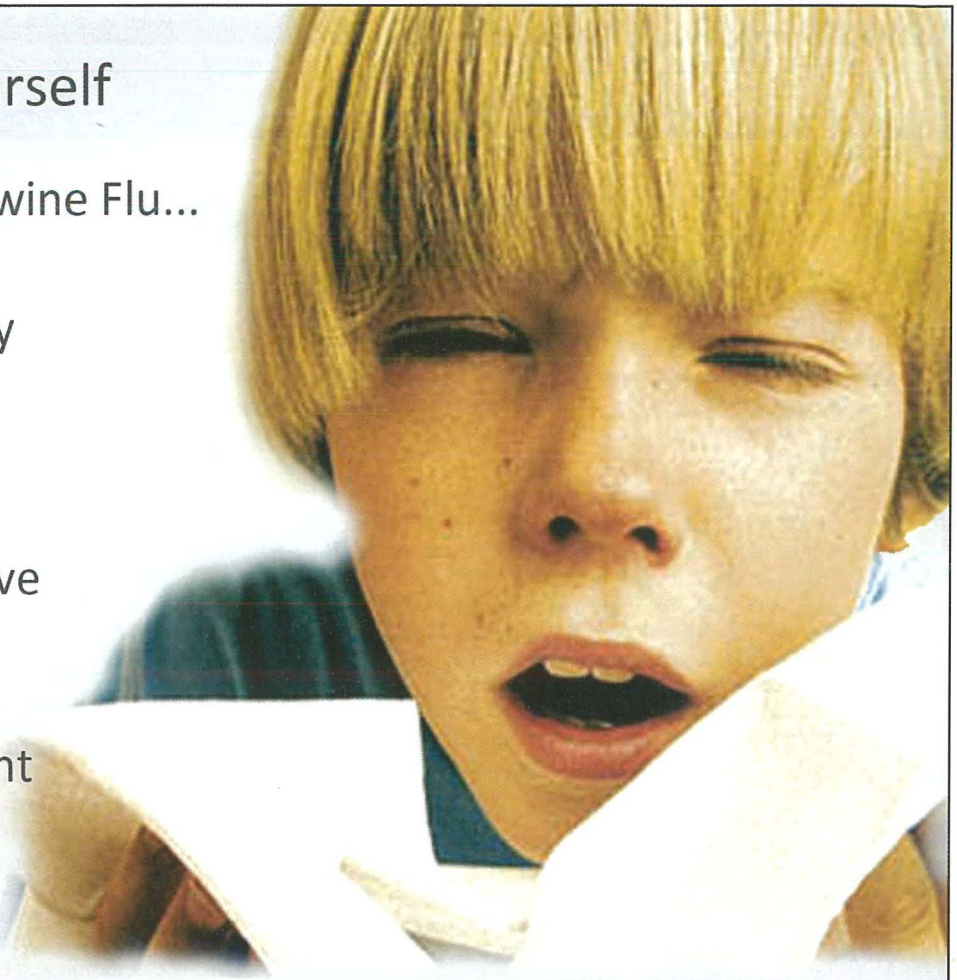


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# Cervical Cancer Screening

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

*The first realization that cervical cancer was a sexually transmitted disease was originally made in the mid-nineteenth century by the Italian chief physician of a Verona hospital and an instructor at the University of Padua, Domenico Antonio Rigoni-Stern.*

In his presentation to the Surgeons' Subgroup of the IV Congress of the Italian Scientists delivered on 23 September 1842, Rigori-Stern reported that in his review of the death registries of the town and suburbs of Verona over a period covering 80 years [1760 – 1839], cancer of the cervix of the uterus was noted to be rare in nuns and unmarried women, but widespread in housewives, suggesting a sexual link with the malignancy. As usually happens with a landmark observation, Rigoni-Stern's observations were completely ignored for the next hundred years. Interest in the aetiology and epidemiology of cervical cancer was revived during the 1940s, when a number of studies confirmed Rigoni-Stern's findings and the general consensus accepted that cervical neoplasia had the characteristics of a venereal transmitted disease. The true causative agent was however only identified in 1976. This cancer appears to be caused by several types of the human papillomavirus (HPV), particularly the subtypes HPV 16, 18, 31 and 45; though a number of other subtypes account for other occasional cases (Figure 1). This virus is introduced into the genital tract during sexual but not necessarily penetrative intercourse; it then resides there causing gradual changes in the cervical epithelium that progress from early cellular changes, to epithelial thickening, to precancerous states and on to full-blown cancer.[1]

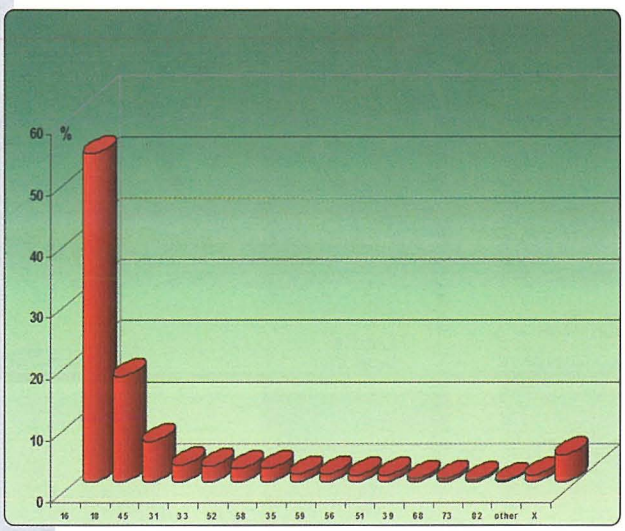


**Figure 1.** *Cervical Cancer attributed to the most frequent HPV types*

Cervical cancer in the world is the fifth most deadly cancer in women; affecting about 1 per 123 women per year and killing about 9 women per 100,000 per year. It is estimated that there are at any one time about 473,000 women affected by the cervical malignancy; more than half will succumb to the disease. The incidence rates of cervical cancer in various populations and communities vary in accordance to the sexual practices of that community, being higher in more promiscuous societies. The incidence of cervical cancer reported in Europe and the Eastern Mediterranean lands varies from the high 27.3 per 100,000 women in Serbia & Montenegro to the low 2 per 100,000 women in the Syrian Arab Republic. The rate in the Maltese Islands was reported at 4.8 per 100,000 women, placing the Maltese population in the ninth place of the European-Middle East low risk chart (Figure 2). It is telling that except for Finland, the eight countries who reported lower rates include populations from the Syrian Arab Republic, Iraq, Qatar, Jordan, Israel, Turkey and Saudi Arabia.[2]

The advent of the sexual revolution in Europe experienced during the "swinging sixties" – delayed in Malta to the 1980s because of the previously strong Roman Catholic moral influence – should have led to an increase in incidence rates in most sexually progressive communities. This rise in incidence rates has been observed but has not been as dramatic as one would have expected because of the contemporary introduction of effective screening programmes. Cervical cancer and precancerous lesions are relatively easy to look out for by visualizing the cervix and sampling the cells from the organ. The national service of population screening for cervical carcinoma was introduced in the government hospitals in 1977 and expanded to the specialist community health centres or polyclinics in 1982. This was complimented by the service offered in the private health sector. The programme however was and remains an opportunistic one whereby it is left to the individual woman to seek screening. Many women fail to get themselves screened or do not screen themselves regularly. The National Health Information Study conducted in 2002 among a randomized sample of the Maltese population has shown that only 45.1% of women interviewed reported having a smear test in the three years prior to the survey; 41.1% reported never having a smear test done and 13.8% reported that the most recent smear was performed more than three years before.[3] The last two decades in Malta have seen a fall in the incidence of cervical cancer but a significant rise in the number of premalignant cervical lesion and HPV-infections. This observation suggests that, in spite of the rather opportunistic screening programme in place on the Islands, the large majority of potentially malignant cases are being identified and treated early before they become fully malignant.

The cervical smear sampling technique was invented by Georgios Papanokolaou in 1928 originally intended to detect cyclical hormonal changes in the vaginal cells and later developed into a cancer screening test in 1941. The test has changed very little since its invention; though the last decade has seen the development of liquid-based cell thin-layer technology which makes interpretation of the smear less susceptible to false results. The test remains an effective, widely used method for early detection of cervical cancer and pre-cancer. There is no definite screening protocol, since this varies from one country to another depending on the health services facilities available in each individual country. Countries with a comprehensive health service, like the United Kingdom, propose a screening protocol based on a balance of clinical risks and cost concerns with the aim of covering a wide section of the population with the least cost. Other countries, often those whose national health service is not comprehensive, recommend more frequent screening. The American guidelines mainly base the recommendations on clinical risk status rather than on cost concerns.

*continues on page 10*

Help X out cervical cancer

# Think long term: Protect them with Cervarix®

ONLY Cervarix® provides high and sustained antibody levels against both oncogenic HPV 16 and 18 for at least 6.4 years[1,2]

CERVARIX ABRIDGED PRESCRIBING INFORMATION: Please refer to the full Summary of Product Characteristics before prescribing. Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu. TRADE NAME: CERVARIX. ACTIVE INGREDIENT: 1 dose (0.5 ml) contains: Human Papillomavirus type 16 L1 protein 20 micrograms, Human Papillomavirus type 18 L1 protein 20 micrograms, (recombinant, adjuvanted, adsorbed). PHARMACEUTICAL FORM: Suspension for injection in prefilled syringe. THERAPEUTIC INDICATIONS: CERVARIX is a vaccine for the prevention of and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. The indication is based on demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years. POSOLOGY AND METHOD OF ADMINISTRATION: The recommended vaccination schedule is 0, 1, 6 months. The need for a booster dose has not been established. It is recommended that subjects who receive a first dose of Cervarix complete the 3-dose vaccination course with Cervarix. Not recommended for use in girls below 10 years of age. Cervarix is for intramuscular injection in the deltoid region. CONTRAINDICATIONS: Hypersensitivity to the active substances or to any of the excipients; acute severe febrile illness. PRECAUTIONS: Anaphylactic reaction; Cervarix should not be administered subcutaneously and never intravascularly or intradermally. Caution in individuals with thrombocytopenia or any coagulation disorder. As with any vaccine, a protective immune response may not be elicited in all vaccinees. Cervarix protects against disease caused by HPV types 16 and 18. Other oncogenic HPV types can also cause cervical cancer and therefore routine cervical screening remains critically important and should follow local recommendations. Cervarix has not been shown to have a therapeutic effect and is therefore not indicated for treatment of cervical cancer, cervical intraepithelial neoplasia (CIN) or any other established HPV-related lesions. Cervarix does not prevent HPV-related lesions in women who are infected with HPV-16 or HPV-18 at the time of vaccination. DRUG INTERACTIONS: Data have not been generated on the concomitant administration of Cervarix and other vaccines. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of Cervarix. In patients receiving immunosuppressive treatment, an adequate response may not be elicited. PREGNANCY AND LACTATION: Vaccination should be postponed until after completion of pregnancy. Cervarix should only be used during breast-feeding when the possible advantages outweigh the possible risks. ADVERSE EVENTS: Common and very common: headache; gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain; itching/pruritus, rash, urticaria; myalgia and arthralgia; injection site reactions including pain, redness, swelling; fatigue; fever ( 38°C); Uncommon: dizziness, upper respiratory tract infection, other injection site reactions such as induration, local paraesthesia. PHARMACOLOGICAL PROPERTIES: *Clinical studies:* The term "premalignant cervical lesions" in section 4.1 of the SPC corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN 2/3).The efficacy of Cervarix was assessed in controlled, double-blind, randomised Phase II (study 001/007) and Phase III (study 008) clinical trials that included a total of 19,778 women aged 15 to 25 years. In study 007, in which a subset of women vaccinated in study 001 was followed up to 6.4 years (approximately 77 months) after the first dose, the efficacy of Cervarix against 12-month persistent HPV-16/18 infection was 100%. In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) and all subjects remained seropositive for both types throughout the follow-up phase (up to month 18), maintaining antibody levels at an order of magnitude above those encountered after natural infection.

Please refer to section 5.1 of the SPC for further information on clinical trials. **PRESENTATION:** Pack of 1 pre-filled syringe with a plunger stopper containing 0.5ml of suspension + 1 needle (refer to full SPC for information on disposal). **LEGAL CATEGORY:** POM. **M.A.HOLDER:** GlaxoSmithKline Biologicals S.A. Belgium. **M.A. NUMBER:** EU/1/07/419/004. *For further information and full prescribing information contact GlaxoSmithKline (Malta) Ltd. Tel: 21 238 131. Date of preparation: September 2008.*

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1. Harper D, Gall S, Naud P, Quint W, Dubin G, Jenkins D, *et al.* Sustained immunogenicity and high efficacy against HPV-16/18 related to cervical neoplasia: long-term follow up through 6.4 years in women vaccinated with Cervarix™ (GSKs HPV 16/18 AS04 candidate vaccine). Society for Gynecologic Oncologists (SGO). Tampa, Florida, USA, 2008, March 9-12.

2. Wheeler C, Teixeira J, Romanowski B, De Carvalho NS, Dubin G, Schuind A. High and sustained HPV-16 and 18 antibody levels through 6.4 years in women vaccinated with Cervarix™ (GSK HPV-16/18 AS04 vaccine). 26th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID). Graz, Austria, 2008, May 13-16.


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# Cervical Cancer Screening

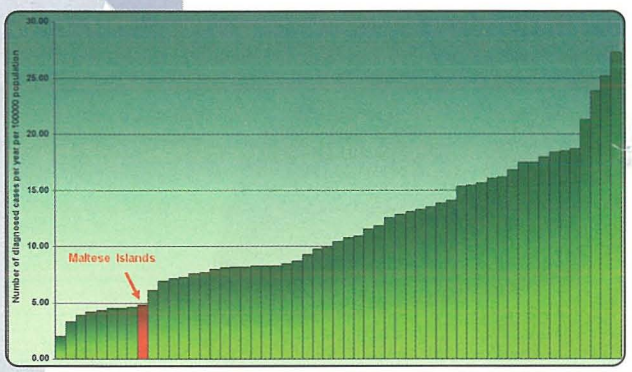


**Figure 2. Incidence Rates of Cervical cancer in the European-Middle East Region in 2002** *(Source: Globocan 2002)*

Women with extremely low risk status – virginal women, after hysterectomy with removal of the cervix, or those aged over 65 years who have had at least 10 normal smears – can opt out from performing regular cervical smears. These extremely low risk women however can still develop different relatively rare forms of cervical cancer which have no relationship to sexual activity.

Those considered to be low risk women – women with less than three sexual lifetime partners, no history of sexually transmitted disease, and onset of sexual activity after 20 years of age – are advised to commence cervical cancer screening at least three years after the first sexual experience, followed up by annual smears until the age of 30 years, and subsequently 2-3 yearly until the age of 65 years. Those women who are known to be at high risk of developing cervical cancer – women with more than three lifetime sexual partners, an early sexual experience, a history of some form of sexually transmitted disease, and a history of an abnormal cervical smear in the past – should opt for an initial twice yearly screening followed by annual testing until there are three consecutive normal results after which they should opt for 2-3 yearly screening until the age of 65 years, provided subsequent smears remain normal.

Cervical screening alone cannot be considered sufficient for diagnosis since false positive results can occur with the crude simple screening test. An abnormal cervical smear result is usually followed by a more detailed examination using a colposcope. This instrument is basically a 'magnifying glass' that allows the clinician to examine the cervix under magnification to identify and biopsy any sites which appear possibly abnormal. A colposcopic service enabling the better investigation and management of premalignant lesions was first introduced in Malta in 1987. The biopsy can then give a more definite diagnosis upon which a clinical decision regarding management can be made. Depending on the severity of the condition, the management can range from regular follow-ups to local destruction of the lesion, to excision of the cervix to an extensive hysterectomy.

All these facilities have helped reduce the mortality of cervical cancer in the Maltese Islands from the level of 4.8 per 100,000 women in the early 1960s to 3 in the early 2000's. This reduction has occurred in spite of the increase in sexual activity which has occurred in the last decades.[4] A recent survey has shown that only 20% of Maltese individuals reported having one sexual partner, 23% reported having had more than 10 partners. The first sexual encounter on average occurs at about 19 years of age; however 22% of girls and 13% of boys had their first sexual encounter by 15 years of age.[5]

The fight against this destructive disease has however been limited in the sense that attempts have been done to identify and treat premalignant conditions early. The screening methods in place therefore help reduce the incidence and hence mortality of cervical cancer; but they do not help reduce the rising incidence of cervical premalignant conditions brought on by an increasing promiscuous lifestyle. They do not offer any prevention against the infection. The breakthrough in prevention has come in recent years by the introduction of specific vaccines to protect against the two subtypes of the HPV most responsible for the development of cervical cancer. Two vaccines have been introduced locally by different companies. Both protect against subtypes HPV 16 and 18 that account for over 70% of cervical cancer cases. They also seem to have crossover cover against other HPV subtypes. Obviously, protective cover is only effective provided the woman has not been previously infected. Hence it is recommended that ideally the vaccine is administered to females before they become sexually active starting by vaccinating children aged 10 years. Because of the rarer forms of HPV subtypes that cause cervical lesions and which are not covered by the vaccine, the administration of the vaccine does not exclude the need for continuing with a scheme of cervical screening. One would hope that the Maltese health authorities will be bold enough to emulate their counterparts in other European countries and introduce the vaccine in the vaccination schedule currently in force. The economic costs of vaccination far outplay the economic, psychological and physical costs of treating cervical premalignant and malignant lesions.

## References

**1.** Kaufman RH, Adam E. Herpes simplex virus and human papilloma virus in the development of cervical carcinoma. *Clinical Obstetrics and Gynecology* 1986; 29:678-92.

**2.** Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide*. IARC CancerBase No. 5, version 2.0, IARCPress, Lyon, 2004. Accessible from: *http://www-dep.iarc.fr/*

**3.** Department of Health Information. *The First National Health Interview Survey, – Summary Statistics*. FHI, Malta, 2003 [downloaded from *http://www.sahha.gov.mt*].

**4.** Buttigieg GG, Savona-Ventura C, Vella K, Cassar O. Cervical Carcinoma in the Maltese population. *International Journal of Risk and Safety in Medicine* 2008; 20(4):223-30.

**5.** Mifsud M, Buttigieg GG, Savona-Ventura C, Delicata S. Reproductive health in Malta. *The European Journal of Contraception and Reproductive Health Care* 2009; in press.

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**Presentation:** Catafast powder for oral solution in sachets of 50 mg diclofenac potassium. **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 up to 150mg daily. **Children and adolescents below 14 years of age:** not recommended. **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); Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other 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, persistent abnormal liver and renal function tests; 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, chronic infections of the respiratory tract, 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. Combined use with protective agents to be considered in patients with history of ulcers, elderly, and those requiring low dose aspirin. Monitoring of liver function and blood counts recommended during prolonged treatment. 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 defects of haemostasis. As Catafast contains a source of phenylalanine, may be harmful for patients with phenylketonuria. Beware of severe fluid retention and oedema. Very rarely reported serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Discontinue at the first appearance. May be associated with a small increased risk of arterial thrombotic events. Before treatment consider carefully patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease, and before initiating longer-term treatment of patients with risk factors for cardiovascular disease. **Pregnancy and lactation:** 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. Should not be administered during breast feeding in order to avoid undesirable effects in the infant. **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. 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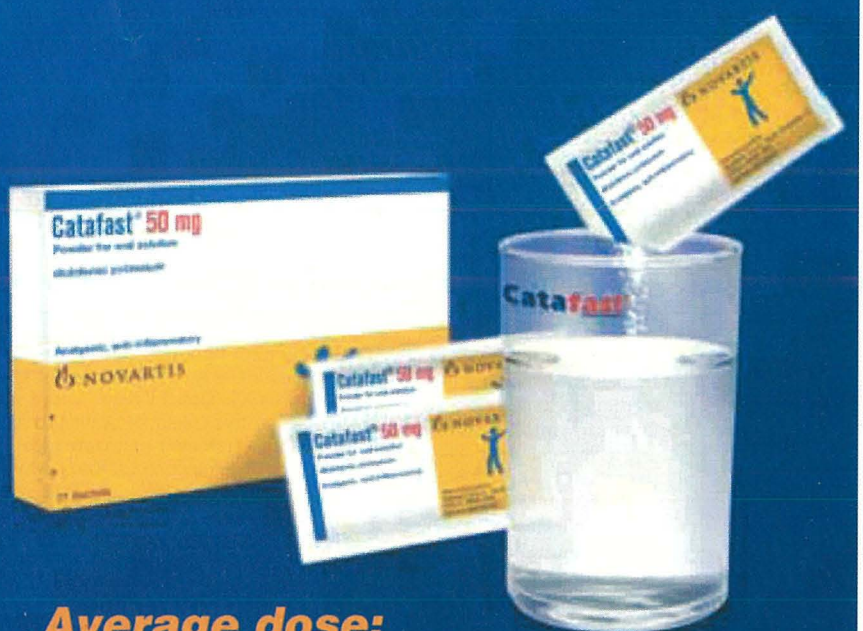


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References

1. Novartis Pharma. Catafast Summary of Product Characteristics.
2. Marzo A et al. Pharmacokinetics of diclofenac after oral administration of its potassium salt in sachet and tablet formulations. ArzneimForsch / Drug Res 2000; 50(I):43-47.
3. Diener HC, Montagna P et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalalgia 2006;26(5):537-47.


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# Letter to the Editor

### Family Medicine crisis?

Currently we are experiencing a drive to replace the doctor – patient relationship where the focus is on emphatic values and personalization of care, with a concept that sharing clinical information through informatic instruments could replace the informal and intimate patient - family doctor relationship.

A case in point is the importance given to the technical, standardized and codified elements in our work, which is distracting us from adequately listening to the patient and treating him/her wholistically. It is well known how the International Classification of Diseases (ICD) codification in its various editions is inadequate within the family medicine's dimension, where we often treat symptoms without actually having a clear diagnosis where frequently time itself is of diagnostic help, during which we prescribe provisional or symptomatic treatments (at times to contain incertainty), or we try to exclude less probable diagnostic possibilities.

It is one matter to hand prescriptions directly to patients who are free to use them as they consider best for them, however it is another matter to transfer such sensitive data to third parties, not related to the therapeutic – assistance relationship. Clearly, consensus by the patient on such data transfer is crucial.

In order to ensure the support of our healthcare systems we will also be shortly experiencing increased pressures to decrease interventions which are not fully supported by scientific evidence. However, interventions supported by studies rarely refer to populations as we meet in the common daily clinic practice since they are conducted in selected groups, free from the co-morbidity's complexity.

In fact if we read carefully several recent scientific papers, we can see that in the family medicine's setting, mainly when concerning chronic social pathologies, it is rare to find interventions with convincing evidence on relevant clinic endpoints.

By reducing the access to family medicine and by eliminating the doctor - patient relationship, we will thus be worsening efficiency and increasing beaurocracy leading to a decrease in equity in healthcare provision.

**Francesco Carelli**
*Professor of Family Medicine, University of Milan*
*International Ambassador Association of Health Care Professionals*

# TheSynapse eQuiz Winner

**The overall prize winner for The Synapse Anthelios eQuiz was Annelise Sapiano.**

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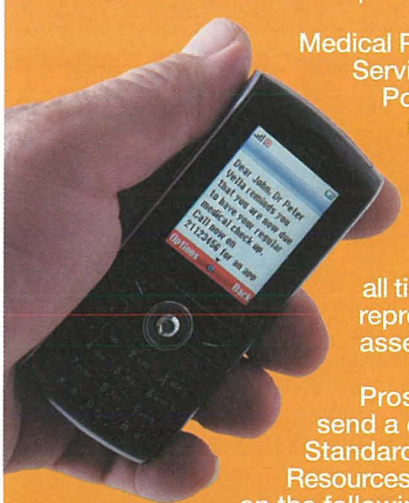

Medical Portals Ltd, operators of TheSYNAPSE Services which includes TheSynapse Web Portal and SMS4Health services, is requesting the service of a part time sales representative. The successful candidate must possess a flair for sales, great interpersonal and communication skills plus the ability to maintain client confidentiality at all times. Previous experience as a medical representative would be considered as an asset.

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**RASILEZ HCT®**
**Presentation:** Film coated tablets containing 300 mg aliskiren (a renin inhibitor) and 12.5 mg hydrochlorothiazide (a thiazide diuretic), or 300 mg aliskiren and 25 mg hydrochlorothiazide. **Indications:** Treatment of essential hypertension. Indicated in patients whose blood pressure is not adequately controlled as on aliskiren or hydrochlorthiazide used alone. Indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose levels as in the combination. **Dosage:** One tablet of Rasilez HCT 300/12.5 mg or 300/25 mg daily. **Contraindications:** ♦ known hypersensitivity to the components of this product or to sulfonamides ♦ history of angioedema with aliskiren ♦ pregnancy and breast-feeding ♦ severe hepatic impairment ♦ severe renal impairment (creatinine clearance < 30 mL/min) ♦ refractory hypokalaemia ♦ hypercalcaemia ♦ concomitant use with ciclosporin and other potent P-gp inhibitors. **Warnings/Precautions:** ♦ Avoid use in women planning to become pregnant ♦ Caution in patients with heart failure ♦ Symptomatic hypotension in sodium- and/or volume-depleted patients which should be corrected prior to initiation of therapy. ♦ Treatment should be discontinued if angioedema occurs and appropriate therapy and monitoring provided until resolution of signs and symptoms. ♦ Caution is advised when administering Rasilez HCT to patients with renal artery stenosis, renal and liver impairment, renovascular hypertension or systemic lupus erythematosus. ♦ Disturbance of serum electrolyte balance including hypokalaemia, hypochloraemic alkalosis, hyponatraemia and hypercalcaemia (monitoring recommended), glucose tolerance and serum levels of cholesterol, tryglicerides and uric acid. ♦ Use with caution in patients with aortic and mitral valve stenosis. ♦ Caution with moderate P-gp inhibitors such as ketoconazole. ♦ Caution with concomittant potassium-sparing diuretics, potassium supplements or potassium-containing salts. ♦ Stop treatment in the event of severe and persitent diarrhea. ♦ Caution in excessive reduction of blood pressure in patients with ischaemic cardiopathy of ischaemic cardiovascular disease.♦ Caution in driving or operating machinery. ♦ Caution with patients with history of allergy and asthma. ♦ Not recommended in patients below 18 years of age. ♦ Excipients: Contains lactose and wheat starch. **Interactions:** ♦ Monitoring when used concomitantly with furosemide, lithium, products affected by serum potassium disturbances (eg digitalis glycosides, antiarrhythmics), calcium supplements or calcium sparing medicinal products ♦ Possible interaction with digoxin, irbesartan, St. John's wort, and rifampicin ♦ Meals with high fat content substantially reduce absorption. ♦ Caution when used concomitantly with drugs that may increase potassium levels (eg potassium supplements, heparin sodium) and drugs that decrease potassium levels (eg corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, laxatives, salicylic acid derivatives, other kaliuretic diuretics); ♦ Caution if combined with other antihypertensives, curare derivatives, NSAIDs (especially in the elderly), digoxin, antidiabetic agents, allopurinol, amantadine, diazoxide, cytotoxic drugs, anticholergenic agents, cholestyramine and colestipol resins, vitamin D, calcium salts, pressor amines, antigout medicine, and ciclosporin. ♦ Caution should be excercised on concomintant use with ketoconazole or other moderate P-gp inhibitors (ketoconazole, itraconazole, clarithromycin, erythromycin, amiodarone, telithromycin). ♦ Grapefruit juice ♦ Alcohol **Adverse reactions:** Common: Diarrhoea **For the aliskiren component,** other reported adverse reactions include: Uncommon: Rash. Rare: Angioedema. Laboratory values: decrease in haemoglobin and haematocrit, increase in serum potassium. **For the hydrochlorothiazide component,** other reported adverse reactions include. Aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia, depression, sleep disturbances, restlessness, light-headedness, vertigo, paraesthesia, dizziness, transient blurred vision, xanthopsia, cardiac arrhythmias, postural hypotension, respiratory distress (including pneumonitis and pulmonary oedema), pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite, jaundice (intrahepatic cholestatic jaundice), anaphylactic reactions, toxic epidermal necrolysis, necrotising angiitis, (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like, reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria, weakness, muscle spasm, interstitial nephritis, renal dysfunction, fever. Laboratory values: electrolyte imbalance, including hypokalaemia and hyponatraemia, hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides **Legal Category:** POM Pack sizes: 7, 28 film-coated tablets **Marketing Authorisation Holder:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom **Marketing Authorisation Numbers:** Rasilez HCT 300/12.5 mg - EU/1/08/491/041-060. Rasilez HCT 300/25 mg - EU/1/08/491/061/080 Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma, P.O. Box 124, Valletta, VLT 1000, Malta. Tel +356 22983217. (vsn 2009-MT- RASHCT April 2009)

**References** : 1. Palatini P, Jung W, Shlyakhto E, et al. *J Hum Hypertens*. 2009: 1-11 online publication, 21 May 2009 2. Villamil A, Chrysant SG, Calhoun D, et al. *J Hypertens*. 2007; 25:217-226.

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# Targeting chemokines: new drugs for old diseases

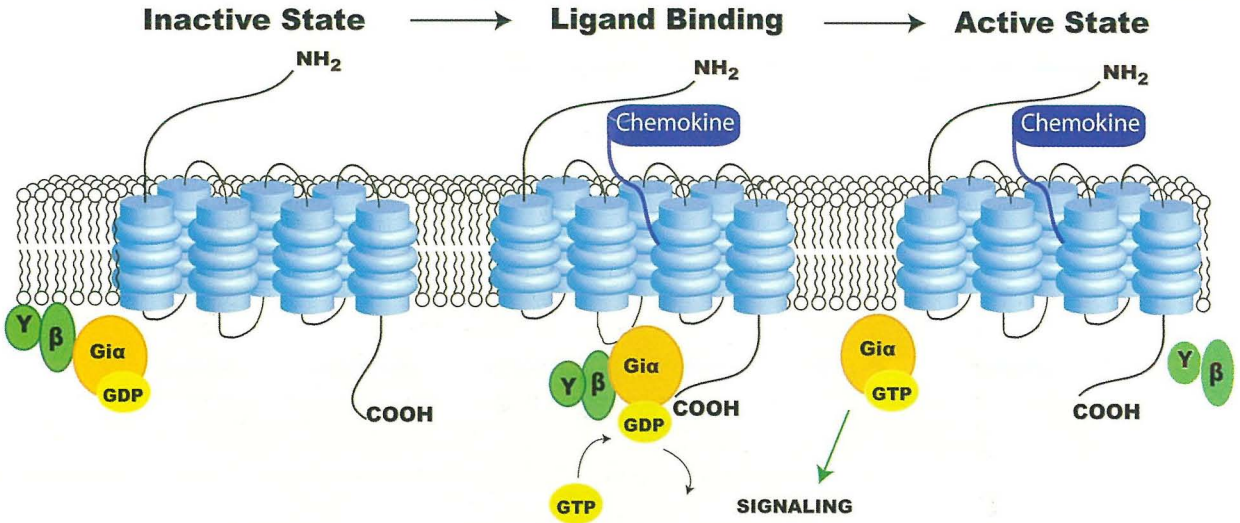


**Figure 2: Chemokine receptor activation**. (Gia-βγ: G-protein, GDP: Guanosine diphosphate, GTP: Guanosine- triphosphate. Adapted from O'Hayre *et al*, 2008.[23])

*continued from page 4*

Chemokine receptors are commonly known to exhibit promiscuity,[5] that is, while certain chemokines show a preference for their own specific receptor; they may also interact with other receptors, causing activation. With the same idea, receptors themselves may also be activated by other, non-specific chemokines. This is known as the *shared receptor concept*, which occurs within, but not between the CC or CXC branches, except for the Duffy antigen/receptor for chemokine (DARC) which binds to the CC and CXC classes with equal affinity.[6] An example of this concept is the chemokine ligand MIP-1α which binds with high affinity to CCR1, CCR3 and CCR5.

## Mode of action

Chemokines act by regulating leukocyte recruitment; causing cellular activation and inflammatory mediator release by promoting the $Th_2$ inflammatory response and by regulating the release of IgE. Their immunomodulatory and chemoattractant action occurs via the infiltration of inflammatory cells and by the inflammatory burst caused from eosinophils and basophils. This causes the migration of leukocytes, a critical component of systemic immunity, from the vascular compartment into the tissues through a process of chemotaxis. This highlights the importance of chemokines as inflammatory mediators as well as the significance of their receptors, the regulation of expression of which is recognised as one of the key events in leukocyte localisation and trafficking during inflammation. Indeed, chemokine expression has been reported to play a major role in (a) glomerulonephritis, (b) inflammatory bowel disease, (c) allergenic transplant rejection, (d) atopic dermatitis, (e) allergic rhinitis, (f) asthma, and (g) chronic obstructive pulmonary disease.[7] This list further includes auto-immune disease such as diabetes and multiple sclerosis, stemming from the fact that chemokines are also able to direct immune cells to target and destroy perfectly healthy cells.

Therefore antagonism of various chemokine receptors has been proposed as a useful therapeutic approach in the management of inflammatory conditions, and indeed several such molecules are currently under development as novel therapeutic agents.[8]

## Chemokine receptor antagonists

The shared receptor concept may make it more beneficial for the pharmaceutical industry to design and produce receptor antagonists, rather than drugs that antagonise the chemokine ligands directly. Indeed various chemokine receptor antagonists are currently being developed as novel therapeutic tools for a variety of diseases. For example, CCR4 antagonists are currently under development for asthma therapeutics. High levels of the CCR4 ligands RANTES, MCP-1, TARC and MDC have been detected in both the sputum and serum of asthmatics.[9] Antagonism of the CCR4, a receptor that has been determined to be a selective marker for $Th_2$ type lymphocytes,[5,10] has been shown to result in decreased eosinophilia and diminished airway hyperresponsivness.[11,12]

It has been recently demonstrated that CCR4 antagonism may be used as a mechanism to inhibit the recruitment of activated leukocytes.[13] These CCR4 antagonists include the neutralising antibody 1G1, which has been shown to potentially block TARC binding to CCR4 transfectants and to prevent chemotaxis of these cells in response to MDC and TARC.[7] Also under development are spironolactams and spiroperidines,[3] a series of 2-aminothiazole derivatives aimed at inhibiting TARC and MDC binding to the CCR4,[14] as well as 2,4-diaminoquinazolines, whose administration in a murine model of acute dermatitis showed significant anti-inflammatory activity.[15]

Other antagonists include the pyrazolone methylamino piperidine derivatives and the patented product GW-766994, both CCR3 antagonists, the latter of which is currently undergoing Phase II clinical trials for the treatment of asthma and allergic rhinitis. Besides having CCR4 antagonistic activity, the spiroperidines also exert a very potent CCR2 blocking action,[16] while the CCR1 antagonist BX471 has been reported to be efficient in a rat heterotrophic heart transplant rejection model.[17]

*continues on page 22*

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# Professor Basant K Puri's Medical School Talk – Part IV
## Attention-Deficit Hyperactivity Disorder

by **Albert Cilia-Vincenti** *MD FRCPath*

*Increasing numbers of children are being diagnosed as having ADHD. The best available treatment has been powerful drugs that help control, but not cure, the worst symptoms. The potential side-effects of these drugs are worrying and the long-term consequences unknown, facing doctors, parents and adult sufferers with a dilemma. Professor Puri looks at ADHD in a different way, starting with brain chemistry and the factors that may influence this. He presents the results of two major studies with which he has been involved and that demonstrate the effectiveness of a completely natural treatment.*

There are several theories about the causes of ADHD and why more people seem to have it. A number of these theories imply that it is not really a medical illness, but may be due to bad parenting, lack of discipline in modern schools, break-up of families, loss of communal religious practice and social cohesion, and to the way our lives have become more complicated and stressful.

Basant Puri's research has shown that ADHD is associated with clear-cut changes in body chemistry which, when treated in a completely natural way, will improve the symptoms and actually cure the disorder, proving that it is a genuine medical illness. Current conventional treatment consists of some form of therapy with powerful psychostimulants such as methylphenidate (Ritalin®) and amphetamine (Adderall® and Dexedrine® - marketed in UK but not in Malta). Many parents of children with ADHD, or adult ADHD sufferers, do not wish to use these powerful drugs, and may not seek help for this reason. Thus many people with this condition, particularly adult sufferers, may not be recognised.

By the 1990s, American schools were reporting many children queuing up every day for stimulant anti-ADHD medication. The increases in production and use of methylphenidate in the US (figure 1) are even more striking when compared to worldwide date (figure 2). In the UK, the National Institute for Clinical Excellence (NICE) has estimated that in a class of 30 pupils, on average one or two children will have ADHD, while in every three classes one child will have severe ADHD (hyperkinetic disorder). True figures might be much higher if many children have indeed not been correctly diagnosed.

ADHD carries enormous financial,

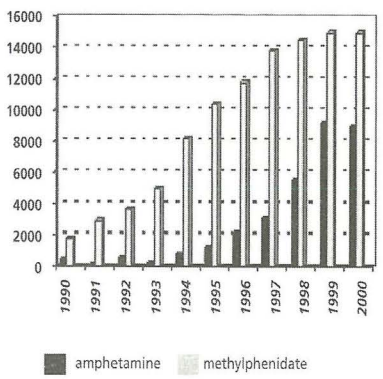


**Figure 1:** *Aggregate production quota in kilograms.*

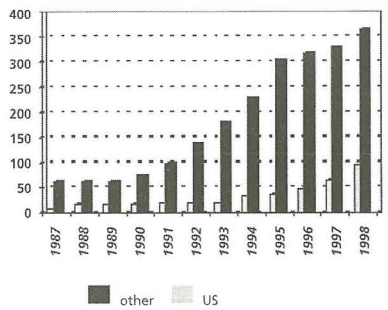


**Figure 2:** *Daily methylphenidate dose in millions of prescriptions.*

social and emotional costs, such as extra specialised school staff, extra home childcare, failure in fulfilling career potential, stress on marriages, educational system burden, in trying to cope with classroom disruptive behaviour, and the individual medical consequences of the stress on the lives of parents and teachers.

Modern research, largely sponsored by pharmaceutical companies, does indicate that this illness has biological causes. Brain neurotransmitters have been found to be abnormal in ADHD. However, the use of psychostimulants came first, and attempts to provide scientific 'justification' for their use followed later. These drugs have helped many children with ADHD, but they carry the risk of unpleasant side-effects. Methylphenidate has similar behaviour to amphetamines – would you give a child some amphetamine or cocaine and not expect unpleasant reactions?

New non-stimulant drugs are being developed for ADHD, the first being atomoxetine hydrochloride (Strattera®), but there are already reports of adverse reactions, including abnormal LFTs, jaundice and hepatitis, with these new drugs. Some parents have therefore turned to the complementary/alternative medicine sector. Avoiding artificial colourings and sweeteners certainly helps, but until Puri's research, there was no scientifically convincing evidence that alternative treatments actually worked.

The cardinal features of ADHD are inattention, hyperactivity and impulsiveness. Different levels of each of these features can appear in different individual sufferers and within each feature, there will likely be differences in the type and/or degree of the symptoms and signs. There are also gender differences, with boys being about 2½ times as likely as girls to suffer from ADHD.

ADHD needs to be differentiated from other disorders, such as autism spectrum disorder, an anxiety disorder or depression, adrenoleucodystrophy (genetic disease affecting males and characterised by abnormal adrenal cortex and brain white matter), and a conduct disorder. The latter is the most difficult to differentiate from ADHD, and some researchers suggest it may be a complication of ADHD. Furthermore, anxiety, depression or a conduct disorder often co-exist with ADHD.

*continues on page 23*

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# Breast Masses in Children - Part I

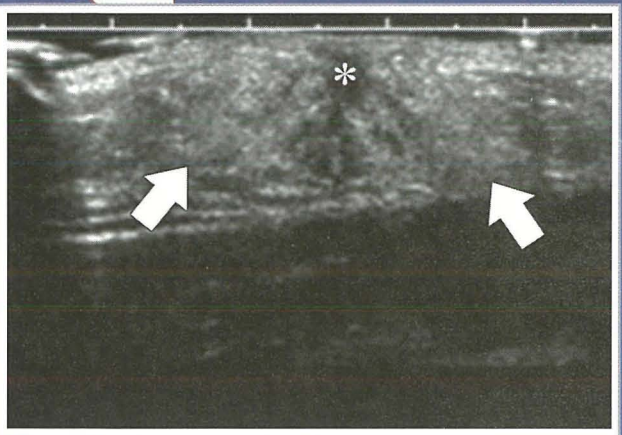

**Figure 1b:** *Tanner stage 2 is characterised by an echogenic nodule with a retroareolar, stellate, hypoechoic focus (*).*

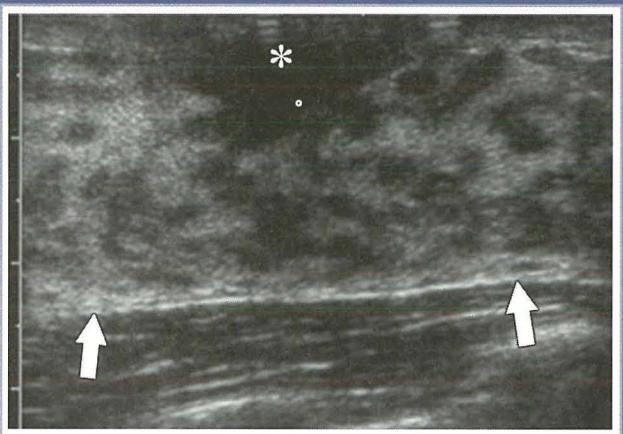

**Figure 1c:** *Tanner stage 3 demonstrates more echogenic, glandular tissue (arrows) with a central spider-shaped hypoechoic focus (*).*

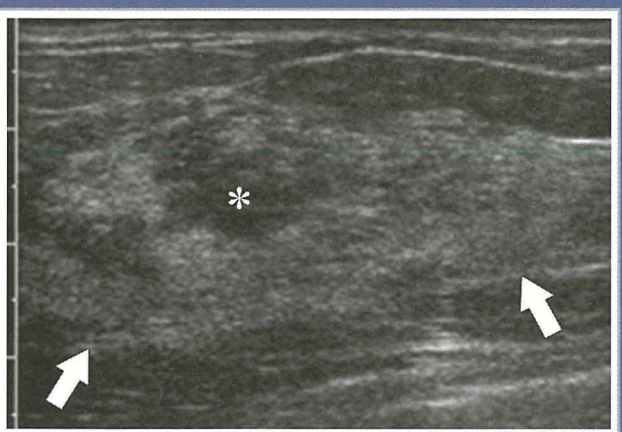

**Figure 1d:** *Tanner stage 4 shows more echogenic fibroglandular tissue (arrows) with a central hypoechoic nodule (*) with increased subcutaneous fat anterior to the glandular tissue.*

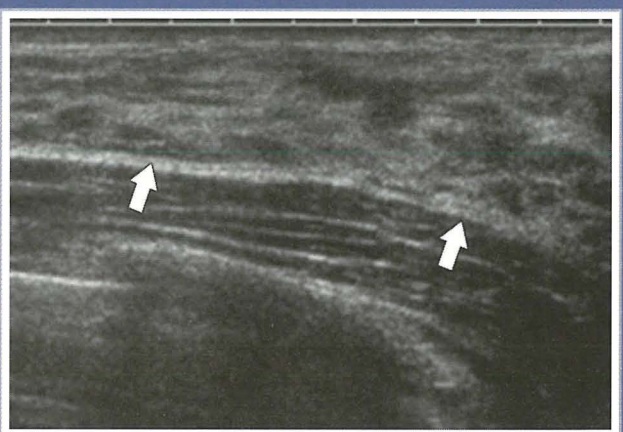

**Figure 1e:** *Tanner stage 5 demonstrates echogenic fibroglandular tissue (arrows) without a central hypoechoic focus.*

Excessive and more rapidly progressive gynaecomastia or development of gynaecomastia in a prepubertal boy suggests the presence of an endocrinopathy or other underlying disease. Uncommon causes of gynaecomastia include oestrogen-producing tumors of the testis, such as Sertoli or Leydig cell tumors; rare, feminizing adrenal cortical tumors; gonadotropin-secreting tumors, such as hepatoblastoma and fibrolamellar carcinoma or choriocarcinoma; prolactinomas; liver disease; Klinefelter syndrome; testicular feminization syndrome; and neurofibromatosis type 1. In addition, use of drugs such as marijuana (Figure 2), anabolic steroids, corticosteroids, cimetidine, digitalis, and tricyclic antidepressants can cause male breast development.

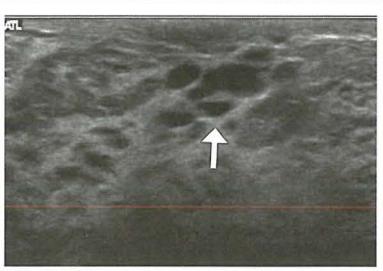

**Figure 2:** *Unilateral gynaecomastia proved after excision biopsy in a 17-year-old adolescent who admitted frequent use of marijuana. Ultrasound scan shows a biconvex focus of decreased echogenicity (arrow) compared with adjacent subcutaneous fat, deep to which is the pectoralis muscle with hypoechoic muscle bundles separated by linear echogenic fascial bands (arrowhead).*

Juvenile hypertrophy, which is also known as virginal hypertrophy or macromastia, is excessive female breast enlargement that occurs in a relatively short period of weeks to months that often begins shortly after menarche but may occur during pregnancy. Usually both breasts are symmetrically, diffusely enlarged, but the condition may be asymmetric or even unilateral. Patients are often very symptomatic, but surgery should be avoided in girls with ongoing breast growth. These patients are generally treated with anti-oestrogen agents, such as tamoxifen. After growth has stabilized, surgical options include reduction mammoplasty and mastectomy with reconstruction.

Premature telarche, gynaecomastia and juvenile hypertrophy all present with ultrasound features of breast development as described in the above Tanner stages with no distinct mass lesion.

Cystic lesions of the breast include duct ectasia, galactocoele, retroareolar Montgomery cysts, abscesses, haematomas and fibrocystic change; with the exception of haematomas, all are uncommon in this age group.

continues on page 22

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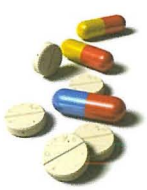

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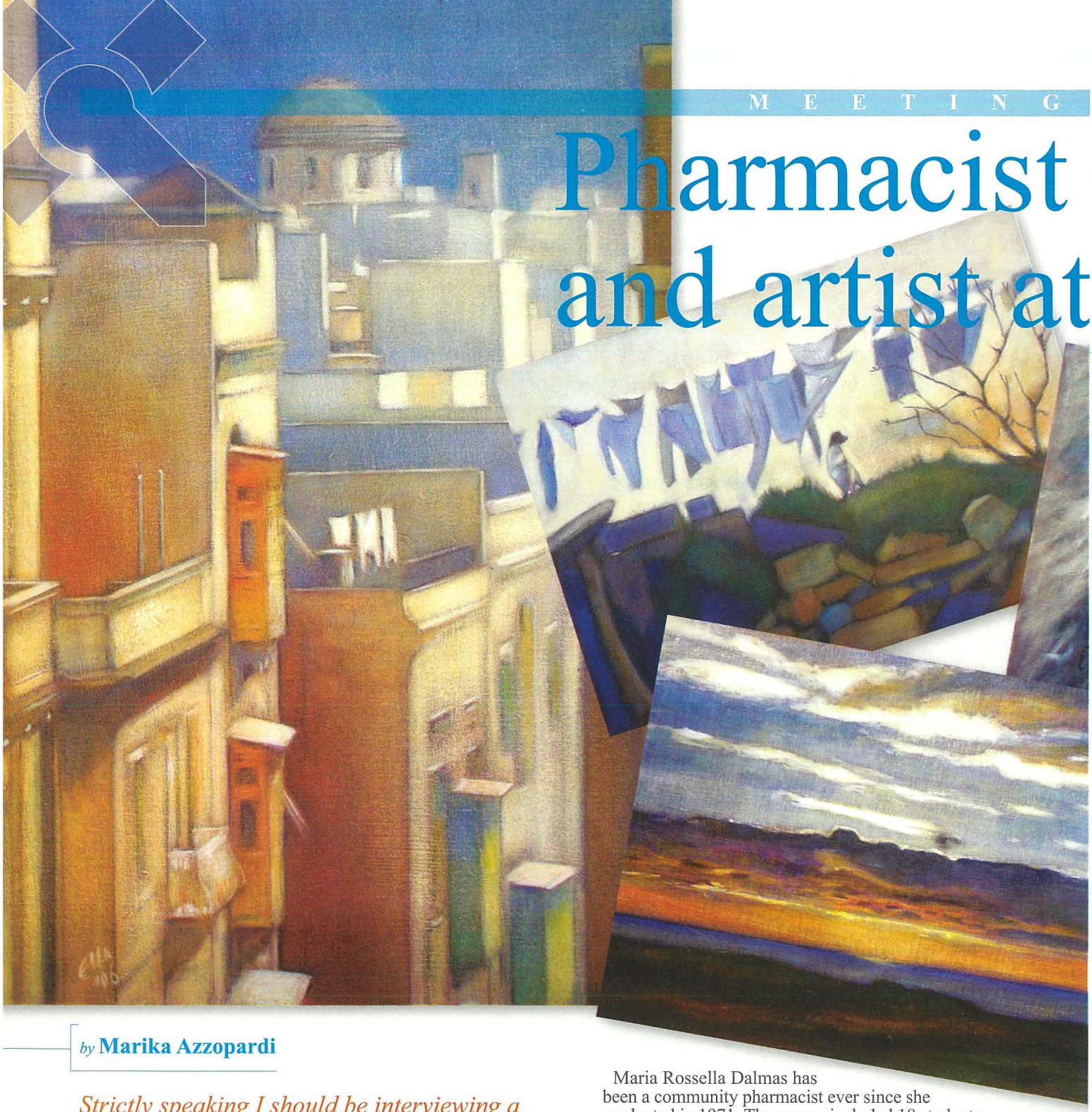
# Pharmacist and artist at



by **Marika Azzopardi**

*Strictly speaking I should be interviewing a pharmacist. And yet, the first thing I get to see are canvases of paintings – beautifully and delicately made scenes of Maltese corners. Not the usual tourist scenes which just about every other artist attempts to experiment with now and again, but snippets of curiosity eked out of your average Maltese streetscape. When considering a 'pjazza' this artist does not take in the architectural details facades, but rather hones in on the most innocuous and probably ignored element of all, focusing on it so intently that it acquires independent aplomb. This is the art of Maria Rossella Dalmas, a pharmacist by profession and an artist at heart.*

Maria Rossella Dalmas has been a community pharmacist ever since she graduated in 1971. The course included 18 students only four of which were male. "There were not many options available at the time. I wanted to become an archaeologist but had to be practical about my choice of career. Archaeology was not considered as an area of study that would earn a woman her livelihood. So it had to be either pharmacy or teaching. Of course I could try becoming a doctor which I absolutely didn't want, or attempt to take up law and become a lawyer which was another no-go area for me. Ultimately I settled for pharmacy."

The choice to become a pharmacist seems to have completely jarred with Mrs Dalmas's natural predisposition for all artistic things. Her father, the late Giuseppe Cassar, was a well-known watercolourist and photographer who inspired her strongly, as did the rest of her artistic relations. From doodling her way throug

# by profession heart

her school days and filling the edges of copybooks with anything that came to her fanciful thoughts, she went on to closely observe the way her father painted as well as the way her aunts combined paint with monochrome photography. "They used transparent oil colours on a sepia base and livened up the flesh colours on face and hands in portraits. The style was very much in vogue and my own graduation portrait is done up like that. I still remember the strong smell of turpentine as they worked."

Today she uses acrylics rather than water colours or oils. She finds these are extremely practical and fast-drying, something which fits excellently with her own fast-paced and busy lifestyle. "There is always very little time to spare in my life, so acrylics it has to be! My father had first bought me poster colours which I didn't particularly like but every child used poster colours to paint back then. I just moved on to acrylics and stayed on using them."

Maria Rossella Dalmas has refined both skill and technique to a point where her streetscapes are imbued with soft colours and uncanny diffusion of light. Canvases are generally extremely smooth-textured and unimpeded by evident brushstrokes, so that her captive moments in time are particularly delicate in quality.

Her last solo exhibition was in June 2007 at Valletta's National Museum of Fine Arts. "I am preparing for another exhibition at the Fine Arts which will be held in November 2011. I feel that my style slowly evolves as I work and am happy with what I have developed. I have moved away from emulating my father's watercolour compositions and now have my distinct style. I know where I want to go and I believe I am making headway in the right direction. But I hope I will never say I have reached my zenith because that would mean a dead-end."

What about pharmacy? How did that change over time and all through these years in the profession? "There have been many, too many changes. We have so many more medicines now than when I was studying or when I started off. Certainly this is owed to great progress in medicine and science. Several things we learnt at University have never been utilised and ultimately there is a big difference between what you are taught and what you use as a community pharmacist. Then again a lot of what we were taught has since been proved wrong. I distinctly remember learning that the intact epidermis is a natural barrier to all sort of medication and that nothing passes through it. That is absolute crap now of course and transdermal patches prove this beyond doubt. Patches are now imbued with all sorts of medications – from nicotine to HRT."

Maria Rossella Dalmas speaks of the requirements of being a good pharmacist, chief of which is the ability to reach out to customers, especially in village pharmacies. "People vary considerably from village to village and from town to village - in the way they speak and reason, and the way they relate to you and treat you. Valletta is an in-between locality, but then you get thrown in at the extremes and that is where the strident differences in people's mentalities and dispositions transpire. Some villagers, especially of the older generation, are not particularly touched by the new levels of education and stick to the old methods which they learnt in their own way. They look to the pharmacist as a consultation post before approaching the doctor. Having said that, they will even trust a pharmacist to the extent of sharing confidential information and trust us implicitly in whatever is related to health matters as well as private affairs, even bringing in personal documents to be read out! We are on the front line always."

# Breast Masses in Children - Part I

Duct ectasia usually presents with nipple discharge (often blood stained) and may progress to mastitis; the tubular nature and continuity of the "cysts" on ultrasound is usually diagnostic (Figure 3). Galactocoeles may be distinguished by the fat/fluid levels both on ultrasound and mammography. Haematomas and abscesses can usually be confirmed on clinical grounds and as with galactocoeles, and may be aspirated for confirmation and treatment. Montgomery's glands are located at the perimeter of the nipple. Ductal obstruction of these glands may result in a debris-containing cystic lesion (<2cm in diameter) that may or may not be painful; the structure is readily evaluated with ultrasound. Fibrocystic changes in the breast are usually physiologic alterations that are very common in the 3rd decade of life, although such changes may be seen to some extent in late adolescence. Patients present with cyclically tender breasts that are nodular on palpation. The findings of fibrocystic change at ultrasound are nonspecific and include multiple cysts of varying sizes, dilated ducts, and echogenic foci representing fibrous tissue that may cause posterior sound attenuation.

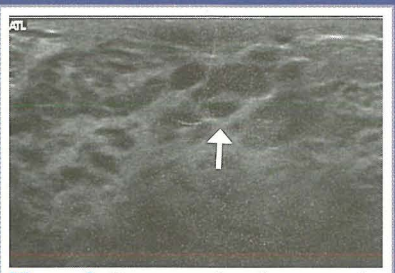


**Figure 3:** *Retroareolar duct ectasia: Ultrasound scan demonstrates dilated anechoic ducts (arrow) seen in cross section deep to the areola.*

*To be continued*

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NEW FRONTIERS IN MEDICINE

*continued from page 14*

# Targeting chemokines: new drugs for old diseases

## Conclusion

Chemokine receptor antagonists therefore have a future in the treatment of inflammatory disease, not only since they seem to modify disease with minimal impact on normal host defence, but also since their action seems to be highly specific with few adverse effects.[18]

The shared receptor concept approach requires the development of antagonists that target a wide variety of receptors at the same time, whose potency would be dependent on the affinity to the receptor and its degree of antagonistic effect. This would avoid the use of complex antagonist mixtures.

Besides the future of chemokine receptor antagonists as anti-inflammatory agents and immunosupressants, one must not fail to mention the advances other types of chemokine antagonists have had in other therapeutic fields. Chemokines have been found to be used by various intracellular pathogens, most notably HIV and *Plasmodium vivax* to facilitate their entry and transmission, and therefore they may represent novel antiviral and antiparasitic treatment. Indeed, TAK-779, the first reported non-peptide antagonist[19] is a CCR5 antagonist that has recently been in Phase I clinical trials as an anti-HIV treatment.[20] More recently reported CCR5 antagonists include UK 427857 (maraviroc),[21] approved by the European Medicines Agency in September 2007, and SCH 351125 (vicriviroc), currently undergoing Phase II clinical trials,[22] all of which contribute to the antiviral therapeutic repertoire.

## References


1. Chemokine Therapeutics Fact Sheet. Available at http://www.chemokine.net/fact_sheet.htm.
2. Melchers F, Rolink AG, Schaniel C. The Role of Chemokines in Regulating Cell Migration during Humoral Immune Responses. *Cell* 1999; 99:351-4.
3. Pease JE, Williams TJ. Chemokines and their receptors in allergic disease. *J Allergy Clin Immunol* 2006; 118:305-18.
4. Murphy PM, Baggiolini M, Charo IF *et al.* International Union of Pharmacology. XXII. Nomenclature for Chemokine Receptors. *Pharmacol Rev* 2000; 52:145-76.
5. Smit JJ, Lukacs NW. A closer look at chemokines and their role in asthmatic responses. *Eur J Pharmacol* 2006; 533:277-88.
6. Horuk R. Chemokine receptors. *Cytokine Growth Factor* Rev 2001; 12:313-35.
7. Chantry D, Burgess LE. Chemokines in Allergy. *Curr Drug Targets Inflamm Allergy* 2002; 1:109-16.
8. United States Trademark and Patent Office. Available at: http://www.uspto.gov/
9. Sekiya T, Yamada H, Yamaguchi M *et al.* Increased Levels of a TH2-type CC Chemokine Thymus and activation regulated chemokine (TARC) in serum and induced sputum of asthmatics. *Allergy* 2002; 57:173-7.
10. Peroni G.D, Bordignon PP, Piacenti L.G *et al.* CC chemokine receptor expression in childhood asthma is influenced by natural allergen exposure. *Pediatr Allergy Immunol* 1996; 17:495-500.
11. Gonzalo JA, Pan y, Lloyd CM *et al.* Mouse monocyte-derived chemokine is involved in airway hyperreactivity and lung inflammation. *J Immunol* 1999; 163:403-11.
12. Kawasasaki S, Takizawa H, Yoneyama H *et al.* Intervention of thymus and activation regulated chemokine attenuates the development of allergic airway inflammation and hyperresponsivness in mice. *J Immunol* 2001; 166:2055-62.
13. Purandare AV, Wan H, Gao A *et al.* Optimization of CCR4 antagonists: Side-chain exploration. *Bioorg Med Chem Lett* 2006; 16:204-7.
14. Wang X, Xu F, Xu Q *et al.* Optimization of 2-aminthiazole derivatives as CCR4 antagonists. *Bioorg Med Chem Lett* 2006; 16:2800-3.
15. Yokoyama K, Ishikawa N, Igarashi S *et al.* Potent CCR4 antagonists: Synthesis, evaluation, and docking study of 2,4-diaminoquinazolines. *Bioorg Med Chem Lett* 2008; 16(17):7968-74.
16. Cascieri MA, Springer MS. The chemokine/chemokine-receptor family: potential and progress for therapeutic interventions. *Curr Opin Chem Biol* 2000; 4:420-7.
17. Horuk R, Clayberger C, Krensky AM *et al.* A non-peptide functional antagonist of the CCR1 chemokine receptor is effective in rat heart transplant rejection. *J Biol Chem* 2000; 275:25562-71.
18. Power CA, Proudfoot AE. The chemokine system: novel broad-spectrum therapeutic targets. *Curr Opin Pharmacol* 2001; 1:417-24.
19. Lagu B, Gerchak C, Pan M *et al.* Potent and selective CC-chemokine receptor-2 (CCR2) antagonists as a potential treatment for asthma. *Bioorg Med Chem Lett* 2007; 17:4382-6.
20. Hayworth B, Lin H, Fidock M, Dorr P, Strange PG. Allosteric effects of antagonists on signaling by the chemokine receptor CCR5. *Bio Pha* 2007; 74:891-7.
21. MacArthur RD, Novack RM. Reviews of anti-infective agents: maraviroc: the first of a new class of antiretroviral agent. *Clin Infect Dis* 2008; 47:236-41.
22. Rollins BJ. Chemokines. *Blood* 1997; 3:909-28
23. O'Hayre M, Salanga CL, Handel TM, Allen SJ. Chemokines and cancer: migration, intracellular signalling and intercellular communication in the microenvironment.. *Biochem J.* 2008;409:635-9.

# Professor Basant K Puri's Medical School Talk – Part IV

## Attention-Deficit Hyperactivity Disorder

Specific learning or language difficulties also tend to co-exist with ADHD, as does developmental coordination disorder, also known as dyspraxia ('minimal brain damage'/'clumsy child syndrome'). Tic disorders may also co-exist with ADHD, and these may take the form of repetitive movements or sounds. Some people with ADHD also appear to have a predilection for abusing illegal drugs. Overall, delays in achieving reading skills or proper motor co-ordination can make it increasingly difficult for affected children to socialize.

Although ADHD and hyperkinetic disorders are currently commonly diagnosed, this was not case until the second half of the 20th century. In 1934, Eugen Kahn and Louis H Cohen described hyperactive (and intelligent) children and adults, and proposed this was caused by a brain stem organic disorder, but this theory did not stand the test of time[1]. Researchers are now more likely to think that the cerebral cortex is more important than the brain stem in causing ADHD.

In 1918, Walter Dandy (professor of neurosurgery at Johns Hopkins, succeeding Harvey Cushing) discovered how to X-ray image the brain ventricles by replacing the CSF with air, a side-effect of which was headaches[2]. Charles Bradley thought Benzedrine® (amphetamine sulphate) might stimulate the brain to produce more CSF after pneumoencephalography to help ease the headaches[3]. He was wrong, but hyperactive children who had been given Benzedrine after this procedure were noted to find it easier to sit still and concentrate in class and, in 1937, he reported that out of 30 children with behavioural problems, 14 showed a 'spectacular change in behavior' and 'remarkably improved school performance'. This is the real foundation for amphetamine and amphetamine-like drugs in children with ADHD.

Neurons communicate via neurotransmitters, which include dopamine, noradrenaline, serotonin, gamma-amino butyric acid (GABA) and glutamate (glutamic acid). Benzedrine® and Ritalin® release dopamine into the synaptic cleft and possibly stop it being removed (figure 3). There is an important pathway containing dopamine brain cells which starts from the brain stem ventral

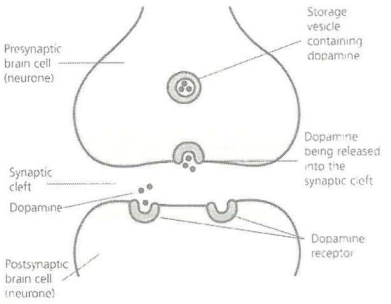


**Figure 3:** *Dopamine neurotransmission*

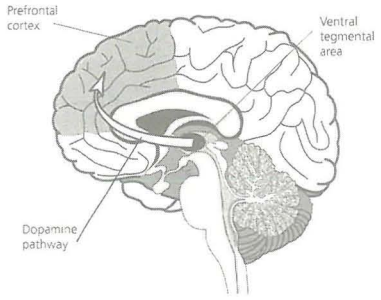


**Figure 4:** *Dopamine pathway*

tegmental area and reaches forward to innervate parts of the frontal lobe and limbic system. The dorsolateral prefrontal cortex may contain some of our 'free will' circuits. The limbic system processes the sense of smell, emotions, learning and memory. The dopamine pathway (figure 4) also innervates the medial prefrontal cortex (mesocortical system). These pathways may also mediate attention, arousal and concentration. Psychostimulants are recommended for ADHD because of their alleged beneficial action on this dopamine pathway.

Genes related to dopamine transmission have also been found to be abnormal in ADHD, but the abnormalities described account for only a tiny fraction of the total genetic component to ADHD. Dopamine is key to pleasure perception. Pleasure centres form part of the brain reward system. ADHD patients have an abnormal brain reward system, making decisions to maximise immediate reward, while ignoring the medium to long-term. Such a 'reward deficiency syndrome' has also been blamed for addiction and pathological gambling. Deficiency of internal brain rewards may instigate seeking substances (alcohol, tobacco, illicit drugs), or behaviours (over-eating, gambling or sexual promiscuity) that release dopamine in brain pleasure centres.

Puri's research into the role of fatty acids in health and disease has led him to the conclusion that many conditions, including ADHD, result from fatty acid deficiencies. The fatty acid model of ADHD[5], put forward by Alex Richardson and Basant Puri in 2000, proposed that at least some features of ADHD may reflect an underlying abnormality of fatty acid metabolism. Viruses, saturated fats, hydrogenated and trans fats, vitamin and mineral cofactor deficiencies, stress hormones and excessive alcohol, can also interfere with fatty acid metabolism.

Production of omega-3 and omega-6 fatty acids influences brain development, including neuronal migration and branching, nerve fibre growth, and the creation, remodelling and pruning of neuronal connections. Fatty acid metabolism defects affect neuronal communication, resulting in cognitive defects or problems with thought processes, such as short-term memory, and attention and concentration, as in ADHD. Abnormalities of dopamine neurotransmission may be involved in ADHD, but the function of all neurotransmitters and their receptors are influenced by the lipid content of the membranes within which those receptors lie. Zimmer and colleagues showed in 2002 that omega-3 fatty acid deficiency in rats is related to dopamine pathway changes resulting in a less active mesocortical system[6]. This confirms that omega-3 deficiency plays a role in impaired dopamine neurotransmission in ADHD. Thus, in the Richardson and Puri fatty acid model of ADHD, ***the fatty acid abnormalities are primary, while the neurotransmitter changes, including dopamine neurotransmission abnormalities, are secondary***.

Mitchell and colleagues, in 1987, compared 48 hyperactive children with 49 normal controls, and found a lower average birth weight and blood omega-3 and omega-6 fatty acids in hyperactive children[7]. Laura Stevens and John Burgess, in 1995, described reduced blood and red cell membrane levels of omega-3 fatty acids in 53 boys with ADHD when compared with 43 normal controls, suggesting a difficulty in converting fatty acid precursors into long-chain polyunsaturated fatty acids such as EPA (*eicosapentaenoic acid*)[8].

*continues on page 24*

# Professor Basant K Puri's Medical School Talk – Part IV
# Attention-Deficit Hyperactivity Disorder

In 1996, the Laura Stevens group found that children with specifically low omega-3 fatty acid levels scored significantly lower on mathematics and overall academic ability. Also in 1996, Bekaroglu and colleagues found significantly lower fatty acid and zinc blood levels in 48 children with ADHD[9]. A lack of zinc can inhibit the omega-3 and omega-6 metabolic pathways. In 2004, Jiun-Rong Chen and colleagues studied 58 children with ADHD and found they had lower omega-3 fatty acid levels compared to normal controls in spite of similar diets, again suggesting a possible problem with essential (short-chain) fatty acids conversion into the long-chain polyunsaturated fatty acids[10]. Also in 2004, Young and colleagues found similar fatty acid results in adult ADHD to those found in childhood ADHD[11].

Ross and colleagues, in 2003, found higher ethane (breakdown product from oxidative damage to omega-3 fatty acids) in exhaled breath of ADHD patients. The evidence for ADHD patients having difficulty synthesizing long-chain polyunsaturated fatty acids, together with evidence that what they can synthesize is broken down too quickly, suggest that the appropriate treatment for ADHD might be supplementation with long-chain polyunsaturated fatty acids.

Several trials of long-chain polyunsaturated fatty acids have taken place. Harding, Judah and Gant showed that huge daily dietary supplementation with vitamins, minerals, amino acids and fatty acids was just as effective as methylphenidate in alleviating ADHD symptoms, but Basant Puri ***does not recommend children or adults with ADHD to take such high doses of vitamins and minerals, some of which, like vitamin A and chromium, might be toxic at those levels***.

Supplementation with evening primrose oil only, or with DHA (omega-6 long-chain polyunsaturated fatty acid docosahexaenoic acid) only, are both ineffective. Furthermore, DHA may have detrimental effects on ADHD symptoms. Richardson and Puri, Richardson and Montgomery, and Portwood, Lowerson and Puri, have shown that EPA with evening primrose oil is an effective way to alleviate ADHD symptoms.

Unfortunately, the regimes used in these studies included DHA. ***DHA is considered not only detrimental to ADHD symptoms, but too much DHA in supplement form may be carcinogenic in the long-term, and should therefore be avoided in supplements***. An over-the-counter supplement is now available (also in Malta) that contains pure EPA, unrefined evening primrose oil and ***no*** DHA.

*In 1918, Walter Dandy discovered how to X-ray image the brain ventricles by replacing the CSF with air, a side-effect of which was headaches ... this is the real foundation for amphetamine and amphetamine-like drug use in children with ADHD*

## References


1. Kahn E, Cohen LH. Organic driveness: A Brain stem syndrome and an experience. NEJM 1934; 210:748-56.
2. Dandy WE. Röntgenography of the brain after the injection of air into the spinal canal. *Annals of Surgery* 1919; 70:397-403.
3. Bradley C. The behaviour of children receiving Benzedrine. *American Journal of Psychiatry* 1937; 94:577-85.
4. Puri BK. Attention-Deficit Hyperactivity Disorder - a natural way to treat ADHD. Hammersmith Press, London 2006, 62-6.
5. Richardson AJ, Puri BK. The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins, Leucotrienes and Essential Fatty Acids* 2000; 63:79-87.
6. Zimmer L, Vancassel S, Cantagrel *et al.* The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *Am J of Clin Nutr* 2002; 75:662-7.
7. Mitchell EA, Aman MG, Turbott SH, Manku. Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clinical Pediatrics* 1987; 26:406-11.
8. Stevens LJ, Zhang W, Peck L *et al.* EFA supplementation in children with inattention, hyperactivity and other disruptive behaviors. *Lipids* 2003; 38:1007-21.
9. Bekaruglu M, Aslan Y, Gedik Y *et al.* Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note. *Journal of Child Psychology and Psychiatry* 1996; 37:225-7.
10. Chen JR, Hsu SF, Hsu CD, Hwang LH, Yang SC. Dietary patterns and blood fatty acid composition in children with attention-deficit hyperactivity disorder in Taiwan. *Journal of Nutritional Biochemistry* 2004; 15:467-72.
11. Young GS, Maharaj NJ, Conquer JA. Blood phospholipids fatty acid analysis of adults with and without attention deficit/hyperactivity disorder. *Lipids* 2004; 39:117-23.


## Bibliography


Arnold LE, Kleykamp D, Votolato NA *et al.* Gamma-linolenic acid dor attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biological Psychiatry* 1989; 25:222-8.
Harding KL, Judah RD, Gant CE. Outcome-based comparisons of Ritalin® versus food-supplement treated children with AD/HD. *Alternative Medicine Review* 2003; 8:319-30.
Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder – a placebo-controlled double-blind study. *European Journal of Clinical Nutrition* 2004; 58:467-73.
Puri BK. The clinical advantages of cold-pressed non-raffinated evening primrose oil over refined preparations. *Medical Hypotheses* 2004; 62:116-8.
Richardson AJ. Clinical trials of fatty acid supplementation in dyslexia and dyspraxia. In Glen I, Horrobin DF, eds *Phospholipid Spectrum Disorder in Psychiatry and Neurology.* 2nd edn. Lancashire: Marius Press; 2003. p. 491-500.
Richardson AJ, Montgomery P. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 2005; 115:1360-6.
Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2002; 26:233-9.
Ross BM, McKenzie I, Glen I, Bennett CP. Increased levels of ethane, a non-invasive marker of n-3 fatty acid oxidation in breath of children with attentiondeficit hyperactivity disorder. *Nutritional Neuroscience* 2003; 6:277-81.
Thorlaksdottir AY, Skuladottir GV, Tryggvadottir L *et al.* Positive association between DNA strand breaks in peripheral blood mononuclear cells and polyunsaturated fatty acids in red blood cells. *Abstracts of the Sixth Congress of the International Society for the Study of Fatty Acids and Lipids.* 2004; Poster (4-5), page 129.
Voigt RG, Llorente AM, Jensen CL *et al.* A randomized, double-blind, placebo-controlled trail of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *Journal of Pediatrics* 2001; 139:189-96.



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