

Clinical Biochemistry News



ACBI



ACB

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Newsletter of the Association of Clinical Biochemists in Ireland
and the Association of Clinical Biochemists (Republic of Ireland Region)



Brian Sheridan awarding the Geraldine Roberts Medal for best poster at ACBI 2007 to Eleanor Lardner (Biochemistry Department, GUH)

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From The President

Dr. Alan Balfé

President of the Association of Clinical Biochemists in Ireland

Top Grade Clinical Biochemist Posts and Training

At the beginning of a new year it is timely to re-focus on the good news that the clinical biochemistry service nationally is in line for a major improvement. In December 2005, Comhairle na nOspidéal (now known as NHO / Comhairle and mandated by statute to regulate and advise on all consultant appointments in Ireland) issued a report on Consultant Chemical Pathology / Top Grade Biochemist Services, with recommendations on the future organisation and development of these services nationally. This report was the result of a review carried out following a request to Comhairle from the Faculty of Pathology of the RCPI. In the consultation process, submissions were invited from each health board and voluntary hospital, and from the professional bodies. Detailed written submissions were made by the ACBI, the Chemical Pathologists, and by the Faculty of Pathologists, and the Comhairle committee met formally with each of these groups.

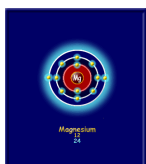
In the report, Comhairle strongly endorsed the complementary roles of Top Grade Biochemist and Consultant Chemical Pathologist, and said that clinical biochemistry departments should be staffed by both specialists working alongside one another. In recommending a substantial increase in the number of these posts nationally, from 11 to 27, it adopted the model of clinical biochemistry departments being staffed by one Consultant Chemical Pathologist and one Top Grade Biochemist working alongside one another. Comhairle also recommended that outreach services would be provided from the local regional hospital to smaller hospitals which did not have either a Consultant Chemical Pathologist or Top Grade Biochemist.

In an appendix to the report, the HSE has specified that the following qualifications shall apply to posts of Top Grade Biochemist in the public health service: the possession of a Ph.D. degree in Biochemistry of a recognised university or the MRCPPath., or a qualification in clinical

biochemistry equivalent to either of these, and eight years post-graduate experience/training including five years in clinical biochemistry.

The ACBI has been running a tutorial scheme for over 10 years to assist biochemists and chemical pathologists preparing to sit the MRCPPath. In its 1997 submission to the Expert Group, the Biochemists' Vocational Group of IMPACT, along with the ACBI, sought funding for training for clinical biochemists. In 2004, arising from discussions with the Department of Health and Children, which were recommended in the report of the Expert Group, interim funding was secured to assist biochemists preparing for the MRCPPath. examination to attend training courses run by the ACB in the UK. These initiatives have borne fruit in terms of considerable numbers of Irish clinical biochemists who have passed Part I and final MRCPPath. examinations, with others currently following in their steps. An application for renewed funding is now with the Department/HSE.

So the posts have been recommended and there are suitably qualified and trained clinical biochemists available to take them up. The Comhairle report identified five of the sixteen new posts as immediate priorities. In addition, several of the established Top Grade Biochemist positions (included in the base of 11 posts enumerated in the Comhairle report) are currently vacant. In 2006, the ACBI proposed discussions with the Chemical Pathologists on the implementation of the Comhairle report, and in early 2007, we sought a meeting with the HSE to discuss the implementation of the report. Progress has been stalled pending the completion of the protracted negotiations on a new consultant contract. We are now hopeful that we will soon be in fruitful discussions with the HSE and with the Chemical Pathologists, leading to the comprehensive national consultant network for clinical biochemistry recommended by Comhairle.



Magnesium - Affairs of the Heart

By Dr Sean Maguire
Mater Hospital
Dublin

In 1991 MF Ryan reviewed the role of magnesium in Clinical Biochemistry in the *Annals of Clinical Biochemistry* (28 (1):19-26). Since then magnesium seems to have become even more important with time. Wael et al, in the *Journal of the American College of Nutrition*, (2004; 23 [1]:63-70 2004) concluded that the intake of magnesium may have a modest inverse association with risk of CHD among men. A total of 39,633 men who returned dietary questionnaires in 1986 were followed up for 12 years. Intakes of magnesium, zinc and potassium and other nutrients were assessed in 1986, 1990 and 1994. Total CHD incidence (nonfatal myocardial infarction (MI) and fatal CHD) was ascertained by biennial questionnaire and mortality surveillance confirmed by medical record review. Standard CHD risk factors were recorded biennially. They found that during the 12 years of follow-up (414,285 person-years), 1,449 cases of total CHD (1,021 non-fatal MI cases, and 428 fatal CHD) were documented. The age-adjusted relative risk (RR) of developing CHD in the highest quintile (median intake = 457 mg/day) compared with the lowest quintile (median intake = 269 mg/day) was 0.73 (95% CI 0.62–0.87, p for trend <0.0001). After controlling for standard CHD risk factors and dietary factors, the RR for developing CHD among men in the highest total magnesium intake quintile compared with those in the lowest was 0.82 (95% CI 0.65–1.05, p for trend = 0.08). For supplemental magnesium intake, the RR comparing the highest quintile to non-supplement users was 0.77 (95% CI 0.56–1.06, p for trend = 0.14).

Magnesium is a coenzyme essential to numerous cellular processes and it modulates the electrical conduction of the heart and its contractility. Magnesium deficiency, though often caused by cardiac surgery, may not be readily diagnosed. Its metabolism may be deranged by effect of cardiopulmonary bypass, by increased excretion and by the secondary effects of the neuroendocrine response to surgery. These changes induce both cardiac symptoms evident as arrhythmias and reduced cardiac function, and neurological disturbances. Active management of magnesium metabolism can ameliorate many of the shifts in electrolyte balance and the resultant problems. In addition, magnesium may be administered as a pharmacological agent to inhibit the myocardial injury that arises during periods of ischaemia (*Journal of Clinical and Basic Cardiology* 2002; (1): 67-73)

Another centre concluded that magnesium sulphate is an effective and safe antiarrhythmic agent for arrhythmias developed after open-heart surgery. Its antiarrhythmic effect may relate to its pharmacological properties and is unrelated to normalisation of the circulating magnesium concentrations. Magnesium sulphate is recommended as a first line antiarrhythmic agent without routine measurement of blood levels (*International Journal of Cardiology* 2003; 89 (2):153-158).

A meta-analysis of randomized clinical trials to examine the effect of magnesium supplementation on blood pressure in the *American Journal of Hypertension* (2002; 15: 691–696) detected significant, dose-dependent BP reductions from magnesium supplementation. However it was concluded that there is still considerable uncertainty on the clinical utility of magnesium supplements. Adequately powered trials with sufficiently high doses of magnesium supplements need to be performed to confirm the inverse dose-response relationship observed in this study.

Members' Publications

O'Hanlon R, O'Shea P, Ledwidge M, O'Loughlin C, Lange S, Conlon C, Phelan D, **Cunningham S**, McDonald K. The Biological variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. J Card Fail. 2007 Feb;13(1):50-5.

Ryan S, Nolan GM, Hannigan E, **Cunningham S**, Taylor C, McNicholas WT. Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. Thorax. 2007 June;62(6):509-14. Epub 2007 Jan 24.

O'Sullivan M, Nic Suibhne T, **Cox G**, **Healy M**, O'Morain C. High prevalence of vitamin D insufficiency in healthy Irish adults. Ir J Med Sci. 2008 Feb 15 [Epub ahead of print].

Duffy MJ, McGowan PM, Gallagher WM. Cancer invasion and metastasis: changing views. 2008;214(3):283-293.

O'Brien N, O'Donovan N, Foley D, Hill AD, McDermott E, O'Higgins N, **Duffy MJ**. Use of a Panel of Novel Genes for Differentiating Breast Cancer from Non-Breast Tissues. Tumour Biol. 2008 Feb 5;28(6):312-317 [Epub ahead of print].

O'Broin SD, Kelleher BP. A dried serum spot assay for vitamin B(12). Clin Chem Lab Med. 2008;46(3):354-8.

Report from Regional Tutor

The MRCPPath trainee group continues to meet approximately monthly. Dates for forthcoming meetings are: Tue, April 8th. Prof. Philip Mayne will speak on biochemistry of the acutely ill child. Wed, May 7th. Dr. Barry Kelleher (Consultant Hepatologist) will speak on laboratory aspects (especially biochemistry) of Liver Disease.

The overall group of trainees now comprises two sub-groups – those who have DipRCPath, and who are at various stages of progress to Part 2 success, and a second group, mainly of newcomers, who are earlier in the path to the Part 1 written exams.

Speaking of written exams the past year has seen a major change in the format of the written papers. The format had been two papers of three hours each paper and that aspect remains. Now, however, instead of both papers requiring you to answer four out of 5 essay questions, the essay questions will be on just one paper. Paper 1 will now comprise six essay questions, with four to be answered. Paper two is where the big change is. The details on the RCPath web site are

‘Paper 2 consists of 20 compulsory Short Answer Questions (SAQs), to be answered in three hours. SAQs are designed to test factual knowledge and understanding across the range of the Curriculum. Each question comprises a stem and six sub-questions. The stem defines the topic of the question and may include a short scenario or vignette. Each sub question is designed to elicit a specific piece of information, or demonstration of understanding of the topic and its context. Unless stated otherwise, the answer required will relate specifically to the material provided in the stem and not to the topic in general.’

This new question format is part of changes being made in all Royal College exams in order to make them less subjective and also to cover more of the curriculum in each exam. It will be interesting to see how this all evolves.

Dr. Peadar McGing, ROI Regional Tutor, Royal College of Pathologists

ACB ROI Region**Report of Scientific Meeting****By Ger Collier Chairperson ACB ROI Region**

Our 4th Regional meeting took place on the 25th of January, 2008 in St. Vincent's University Hospital, Dublin. We were feeling fairly confident that all angles had been covered and the day would go off without a hitch. However, our optimism was short lived when on the morning of the meeting, we realised that one of our speakers was at that very moment skiing down the slopes in Austria, another speaker dashed home to rescue a presentation which he couldn't open on the PC while alas the memory stick of a third speaker failed to accompany him off the plane and was now jetting its way back to the UK. While mere mortals would have panicked, the local organising committee took it all in their stride and by the end of the day a Phoenix had indeed risen from the ashes.

Professor Joe Duffy, St. Vincent's Hospital, bravely stepped into the breach at very short notice and the morning session, chaired by Dr. Peadar McGing, got off to a flying start with a review of urokinase plasminogen activator (uPA). Over the last 20 years Professor Duffy and his team have investigated the role of uPA in breast cancer. Early animal studies suggested that uPA was causally involved in the processes of invasion and metastases suggesting that circulating levels of uPA may predict tumour metastatic potential. In 1988 Professor Duffy's research demonstrated that uPA was indeed a prognostic indicator in breast cancer. The prognostic value of uPA is stronger than markers such as ER, PR, HER2 and EGFR. Plasminogen-Activator-Inhibitor-1 (PAI-1) is an inhibitor of uPA. In node negative patients only a minority will benefit from chemotherapy and most will suffer toxic side effects. Low levels of uPA and PAI-1 are associated with sufficient low risk of recurrence that chemotherapy will only contribute minimal additional benefit. The American Society of Clinical Oncology has now recommended that uPA and PAI-1, measured by ELISA, may be used to determine prognosis in patients with newly diagnosed node negative breast cancer.

Following on, Professor Aiden McCormick, St. Vincent's Hospital, presented a review of liver transplantation. Over the last few years the prevalence of liver disease has increased due to obesity, hepatitis C infection and alcohol consumption. The minimal criteria for transplant listing are less than a 50% survival at 2 years. In end stage liver disease the M.E.L.D score is used

for transplant listing. This score includes assessments of the INR, bilirubin and creatinine. In the case of hepatitis A and paracetamol overdose it is important to recognise patients who may require a transplant, as some recover spontaneously. In these cases the criteria issued by King's Hospital London are used and include measurement of pH, prothrombin time, lactate and creatinine levels together with the grade of encephalopathy. Immunosuppressive therapy has improved over the years and liver rejection is rare. However, renal failure is still a serious complication. Post transplant reinfection by hepatitis C is also still a problem and is associated with poor survival rates and it seems that the age of the donor liver is a predisposing factor.

Professor Mc Elvaney and Dr. Tomas Carroll, Beaumont Hospital, gave presentations on alpha one antitrypsin (AAT) deficiency. AAT is produced in the liver and acts as a protease inhibitor in the lung. M is the normal AAT protein and Z is the most common variant. Z variants fold incorrectly and polymerise in the liver, preventing their release, with concomitant reduced blood and lung levels. In the liver you get gain of toxic function and most heterozygotes have normal AAT levels so the phenotype is required. In the lung loss of function is the result and damage is caused by the chronic burden of neutrophil elastase on the respiratory epithelial surface. The World Health Organisation recommends the screening of all patients with chronic obstructive airway disease for AAT deficiency.

Lunch was kindly sponsored by Roche Diagnostics and even though there was a moment when it looked like congealed Thai Curry and cold rice would be the dish of the day, thankfully it wasn't to be.

Dr. Sean Cunningham chaired the session after lunch, which started with Dr. Julian Barth (Leeds Teaching Hospitals) providing thought provoking insights on key issues concerning reference intervals. Factors such as method bias, population variables together with pre-analytical factors all exert an impact on reference intervals. There are many advantages for the introduction and use of common reference ranges - the widespread use of Electronic Patient Records, advances in assay standardisation, inability of labs to generate their

own reference intervals and in particular the issue that patient care may be compromised by non-comparability of results. Counter arguments against the introduction of common reference ranges would be lack of homogeneity in the population, true standardisation differences for certain analytes and lack of availability of normative data for some analytes e.g. CSF. Dr. Barth welcomed the ongoing projects, which are addressing the need for harmonisation of reference ranges e.g. the Nordic Project and the Pathology Harmony Project set up by Dr. Jonathan Berg.

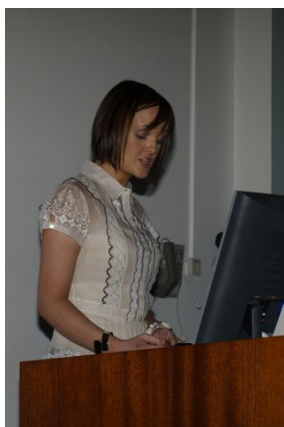
As we face changes in government policy promoting co-localisation of new private hospitals on public hospital sites together with a reconfiguration of Pathology Services in Ireland we were very interested in hearing what Dr. John Land, Whitfield Street Laboratory, London had to say on public and private partnership in the health service. Dr. Land reported on the drivers for change within the laboratories of the UCLH group and the vision to create “an academically driven pathology service with strong clinical leadership and a beacon of modernisation.” Together with their partner

Sonic Healthcare, plus clear objectives, a focused business model, a willingness to embrace change and automation Dr. Land and his team have transformed what was *The Doctor's Laboratory* into a state of the art facility that clearly works and that most organisations would envy.

Last but not least Finlay MacKenzie (UKNEQAS) gave us his valuable opinion on ‘Guidelines’ and the trouble they may cause from a clinical biochemistry viewpoint. The need for consultation with the appropriate professionals, the use of ‘evidence based’ medicine, an awareness of the implementation of certain guidelines on finance, are factors which should be addressed to avoid shortcomings in the whole guideline process.

We would like to thank all our speakers especially Julian Barth who came to Dublin despite his pain! We would also like to apologise to John Land who eventually got back to the UK despite the best efforts of the “Homeland Security” in Dublin Airport who endeavoured to detain him after they had mistaken the ticking of the clock we presented to him as a ‘suspect’ device.

Some photos from the ACB ROI Region meeting



Commentary on the National Academy of Clinical Biochemistry (NACB) Guidelines for Utilisation of Biochemical Markers in Acute Coronary Syndromes & Heart Failure.

Dr. Sean Cunningham, St. Vincent's University Hospital, Dublin

The 1st NACB Guidelines for the use of Cardiac Markers in Coronary Artery Diseases were published in July 1999. Not only are these Guidelines revised, but the scope of the recommendations has been extended considerably beyond that of myocardial necrosis. The NACB 2007 recommendations include Clinical Utilisation of Biochemical Markers in Acute Coronary Syndromes (ACS) and analytical issues relating to these markers, Point-of-Care Testing, Clinical Utilisation of Biochemical Markers of Heart Failure and analytical issues in relation to these. The Guidelines now address issues which were uncertain or problematic following the first guidelines and the publication of the joint ESC/ACC Guideline on the Re-definition of Myocardial Infarction in 2002 (Eur Heart J, 21: 1502 – 13). These were issues such as identification of an MI in patients following percutaneous coronary intervention and coronary artery bypass graft and the elevated Troponin levels frequently observed in in-patients with advanced renal failure. The Guidelines are available on the NACB Website (<http://www.aacc.org/AACC/members/nacb/LMPG/>) and published in chapters in Clinical Chemistry and Circulation journals during 2007.

Recommendations for use of Biochemical Markers for Diagnosis of Myocardial Infarction (MI)

- The patient's clinical presentation (history, physical exam) and ECG should be used in conjunction with Biomarkers in the diagnostic evaluation of suspected MI (Level of evidence I, C. See Footnote*)
- Cardiac Troponin (cTn) is the preferred marker for the diagnosis of MI (I, A).
- Blood for testing should usually be obtained at hospital presentation and at 6 – 9 hours (I, C).
- In the presence of a clinical history suggestive of ACS, the following are considered indicative of myocardial necrosis consistent with MI (I, C).

- a. cTn level exceeding the 99th percentile of values for a reference control group on at least one occasion during the first 24hrs after the clinical event.
- b. CK-MB exceeding the 99th percentile of values for gender specific reference control group on two successive samples (values for CK-MB should rise and/or fall)

For patients presenting acutely in an ischaemic setting, the need to demonstrate a rise and fall in Troponin has been de-emphasised in these guidelines. The single decision limit (99th percentile) for Troponin is now universally recommended.

The section on Analytical Biomarker Issues deals with issues that need to be considered by manufacturers and labs setting up assays, such as establishing the 99th percentile, measuring imprecision, validation of specimen type, detection limit, interferences etc. It is recommended that assays should have a total imprecision (%CV) of $\leq 10\%$ at the 99th percentile. An IFCC study in 2004 (Panteghini et al, Clin Chem 50:327-332) found that many assays were unable to achieve the 10% goal, but some assays have improved since then. Expert consensus now favours the use of the 99th percentile cut-off for Troponin even if the imprecision is not $\leq 10\%$.

Additional recommendations:

- For patients who present within 6 hours of the onset of symptoms, an early marker of myocardial necrosis may be considered in addition to cardiac Troponin. Myoglobin is the most extensively studied marker for this purpose (level of evidence (IIb, B)).
- Total CK, CK-MB Activity, AST, and/or LDH should not be used as Biomarkers for the diagnosis of MI (III, C).

- CK-MB is the preferred marker for detection of reinfarction early after the index event when Troponin is still increased.

Universal Definition of Myocardial Infarction:

It is relevant to note here that a Universal Definition of Myocardial Infarction has recently been published (Circulation, published on-line November 27th 2007, vol.116:2634-53) jointly by an ESC/ACCF/AHA/WHF Task Force.

According to this definition, the criteria for acute myocardial infarction in the patient presenting with a new cardiac event are (in part):

Detection of a rise and/or fall of cardiac biomarkers (preferably Troponin) with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following:

- Symptoms of ischaemia
- ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block)
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

The NACB 2007 guidelines are consistent with this universal definition of MI.

Problematical areas:

Chapter 6 deals with a number of previously unclear or problematical areas and also includes an extensive list of causes of elevated cTn without overt ischaemic heart disease.

- a) Chronic renal failure: Many patients with ESRD have increased baseline Troponin T, and less frequently, increased Troponin I, sufficiently high to meet the MI criteria, without having an acute MI. However it has been established that these patients have a higher risk of cardiac events than ESRD patients with normal troponin. NACB now recommend that patients with ESRD who present with possible ACS and elevated troponin, should have a dynamic change in troponin of 20% before diagnosis of AMI (level of evidence I, B).

- b) Percutaneous coronary intervention (PCI) and cardiac surgery (eg CABG)

Troponin release following PCI occurs in 14-45% of patients. The prognostic usefulness of troponin values post PCI has been questioned when baseline cTroponin is raised. It appears that it is the pre-PCI value which is predictive. Therefore NACB recommend that it is useful to measure cTn before and after PCI if the baseline value is below the 99th percentile. Any increase is indicative of cardiac damage but they find there is insufficient evidence to recommend a specific cut-off (IIb, C). Post CABG, the higher the cTn value the greater the risk of adverse cardiac events. A 5-fold increase in cTn after CABG, together with other clinical parameters, is the cut-off to distinguish between surgical procedure and a vascular event (IIa, C).

Biochemical markers of Ischaemia

About half of patients with definite ACS do not have elevated troponin at initial presentation. Some present early after the onset of acute MI before Troponin is raised, while others present with acute myocardial ischaemia without necrosis (i.e. unstable angina). A Biomarker that reliably detects Myocardial Ischaemia, either in the absence of necrosis or before cTn is increased, would have the potential for early discrimination of these patients from those with chest pain of a non-ischaemic ideology. Markers which have been studied to date include Ischaemia Modified Albumin (IMA), unbound free fatty acids, and whole blood choline. IMA has been the most thoroughly studied. While some claims have been made for its usefulness, others including the authors laboratory have not found IMA to be useful. One problem is that IMA levels are influenced by the concentration of albumin.

IMA appears to be more useful when combined with other markers. This multi-marker approach has also been reported to be useful in studies combining CRP and BNP or NT pro-BNP with Troponin. The NACB Guidelines say that measurement of markers of myocardial ischaemia in addition to cTn and ECG may aid in

excluding ACS in patients with a low clinical probability of myocardial ischaemia (but this is with a low level of evidence, IIb, C).

Early Risk Stratification

There have been many studies which demonstrated that patients with ACS and a raised Troponin had a higher risk of recurrent cardiac events than those without detectable Troponin. Some studies have demonstrated increased risk at higher Troponin levels even within the normal range. (Kontos MC et al, J Am Coll Cardiol 2004; 43, 958-65, Heidenreich PA et al, J Am Coll Cardiol 2001; 38: 478-85).

- NACB recommends that patients with suspected ACS should undergo early risk stratification based on an integrated assessment of symptoms, physical exam findings, ECG findings, and Biomarkers (I, C).
- cTn is the preferred marker for risk stratification. In patients with a clinical syndrome consistent with ACS, a peak concentration exceeding the 99th percentile should be considered indicative of increased risk of death and recurrent ischaemic events (II, A).
- The recommendations state that blood specimens for this purpose should be taken at hospital presentation and at 6 – 9 hours (I, B).. However, there is little if any discussion of the optimal time for risk stratification and the benefit, if any, of using later peak values rather than the 6 – 9 hr value.

BNP and NT pro-BNP are released into plasma and are increased in patients with heart failure due to left ventricular dysfunction, but there is also evidence that these peptides are released in response to ischaemia or hypoxia. There is now considerable data showing a strong association between BNP and NT pro-BNP and mortality in patients with ACS and even in patients with unstable angina and normal left ventricular systolic function.

- Measurement of high sensitivity C-Reactive Protein (hs-CRP), and/or of brain type (B-Type) Natriuretic Peptide (BNP) or N-Terminal Pro-BNP (NT-proBNP) may be useful in addition to a cTn, for risk

assessment in patients with a clinical syndrome consistent with ACS (IIa, A), but management decisions should not be based solely on BNP/ NTproBNP or hsCRP (III, C).

Point of Care Testing and Turn-around time

In general the NACB recommendation for POCT cardiac markers are similar to various guidelines for other POC tests.

NACB recommend that the Laboratory should perform cardiac marker testing with a turnaround time (from blood collection to reporting of results) of 1 hour, optimally 30 minutes (I, B). If this target cannot be consistently met, POC testing should be implemented (IIa, B).

A C.A.P. Q-Probe survey of 159 hospitals in 2004 found that the median and 90th percentile TAT (order to report) for cTn was 75 and 129 minutes, respectively (Novis DA et al, Arch Path Lab Med 128:158-164).

Clinical Utilisation of Biochemical Markers of Heart Failure and related analytical issues

This area will be discussed in a further commentary.

***Footnote:** In these Guidelines, the strength of scientific data supporting each recommendation is characterised using the scoring criteria adopted from the American Heart Association/American College of Cardiology. In this system, recommendations are designated Class I if based upon evidence and/or general agreement that a given procedure or treatment is effective, IIa or IIb if there is conflicting evidence and/or divergence of opinion about its effectiveness and Class III if there is evidence and/or general agreement that it is not effective. Level A recommendations are based on the strongest evidence e.g. from RCTs, Level B are based upon smaller studies and Level C recommendations are based mainly on expert consensus.



Interesting & Useful Websites

Martin Healy

CDC (Centers for Disease Control and Prevention)

<http://www.cdc.gov/>

Full of information for the worrier, traveller, hypochondriac etc. Has information on obscure and not so obscure infections and disease. Want to know about Lassa or Ebola fever then go here. Also has topics on emergency preparedness, environmental health, and healthy living. Thinking of travelling? Then get updates on disease outbreaks, vaccinations, where to avoid. Written from an American perspective but valuable information for all.

National Geographic

<http://www.nationalgeographic.com/>

Species, culture, environment. Photo galleries, video clips. Archaeology, anthropology, cosmology and an excellent kids section. An outstanding educational website.

National Aeronautics and Space Administration (NASA)

<http://www.nasa.gov/>

All things space. Get the latest information on Hubble, Mars Rover, satellites, and the most recent Space Shuttle flight (Endeavour). Live video feeds from shuttle missions can be viewed through NASA TV. Also has a section for kids.

Environmental Health News

<http://www.environmentalhealthnews.org/>

Their aim is to alert us, through links to various publications, to the effects of exposure to chemicals used in the production of everyday items such as tin cans, plastic bottles, babies bottles, toys, cosmetics, shampoos etc etc. All contain chemical agents which leach out and enter our bodies and supposedly cause a variety of disorders. The site offers one side of the argument and is fairly depressing.

BookFinder

<http://www.bookfinder.com/>

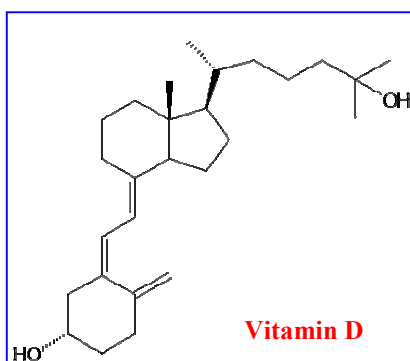
A search engine for books. A simple interface but a powerful tool. Searches over 150 million books by accessing online catalogues of booksellers. Findings listed according to price for both new and used books. Prices displayed include postage costs. If you can't find it here.....

Clinical Analyte Unit Conversion

<http://dwjay.tripod.com/conversion.html>

If you don't carry all of the non-SI to SI conversion factors around in your head then this is the solution. From acetaldehyde to zinc protoporphyrin the site does a quick conversion calculation and provides the factor.

Vitamin D Displays Diversity



We don't get a lot of this in our part of the world. Since ultraviolet light from the sun is essential for activating epidermal production of vitamin D (and allied with the fact that there are few decent dietary sources of the vitamin) it is not surprising that a significant proportion of our population have sub-optimal D vitamin concentrations.

Vitamin D's role in the homeostatic mechanisms of calcium regulation and bone metabolism is well established but more recently research has focussed on possible noncalcaemic roles of the vitamin. A few of these are outlined below.

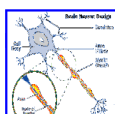
Over the last few of years numerous in vitro and in vivo studies have shown that vitamin D potentially inhibits cell proliferation in a wide range of cell types, including carcinomas of the breast, prostate, colon, skin, and brain, myeloid leukaemia cells, and others. In addition epidemiological studies have demonstrated a relationship between vitamin D status and cancer risk. A recent paper (*What is the Dose-Response Relationship between Vitamin D and Cancer Risk?* Garland CF et al. *Nutrition Reviews* 2007;65(Suppl 1);S91-S95) has shed further light on this issue. The study combined data on average wintertime vitamin D concentrations in 15

countries. They found that there was an inverse relationship between colon and breast cancer rates and average vitamin D concentrations. The protective effect of vitamin D against colon cancer began at concentrations of about 55 nmol/l and for breast cancer at about 80 nmol/l. They estimated the average wintertime concentration of vitamin D in Americans was 37.5 - 45 nmol/l. They go on to say that serum concentrations of at least 137.5 ng/ml would be optimal for cancer prevention. The problem is that few people attain these concentrations particularly those living in northern European countries such as Ireland. The solution is a combination of diet, supplements and 10 - 15 minutes a day in the sun if you can find any. Dermatologists are not happy at the idea of encouraging skin exposure to the sun because of the cancer risk. Also, to achieve the optimal vitamin D concentrations would require a daily intake of 2,000 IU - 5 times the current RDA for adults. The authors are sufficiently confident in their analysis to claim that, worldwide, 250,000 cases of colon cancer and 350,000 cases of breast cancer could be prevented each year provided the optimal concentration of vitamin D could be maintained.



Epidemiologic studies support a protective role for vitamin D in type 1 diabetes, an autoimmune disease. Autoimmunity is driven by T helper lymphocytes, which attack various tissues in the body including pancreatic beta cells. It is likely that the suppression of autoimmune diseases involves vitamin D interaction with these lymphocytes, resulting in a reduction of the inflammatory response. The discovery that vitamin D receptors are expressed in lymphocytes supports this hypothesis (*Noncalcemic Actions of Vitamin D Receptor Ligands*. Sunil Nagpal et al. 2005: *Endocrine Reviews* 26(5):662-687).

Animal studies have demonstrated that vitamin D deficiency accelerates the onset of type I diabetes. In human studies a Finnish birth cohort study demonstrated that vitamin D supplementation during infancy was inversely related to the risk of developing type 1 diabetes. Children receiving 2000 IU vitamin D from age 1 y on decreased their risk of getting type 1 diabetes by 80%. In addition the suspicion of rickets by the age of 2 years increased the risk of later diabetes (*Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study*. Hyponen E et al *Lancet* 2001 Nov 3;358(9292):1500-3).



Multiple sclerosis (MS) is an immune-mediated inflammatory and neurodegenerative condition of the central nervous system. It has long been recognised that the incidence of MS is significantly lower in southern latitudes where there is an abundance of sun. The suggested reason is the UV-generated epithelial production of vitamin D. A

recent study has demonstrated an inverse relationship between serum vitamin D concentrations and risk of developing multiple sclerosis. Working with a repository of stored blood samples from 7 million US army and navy personnel the researchers identified 257 patients who were diagnosed with MS between 1992 and 2004. Vitamin D was measured in these samples and the results divided into quintiles. The results showed that Caucasian patients with highest concentrations of the vitamin - particularly before the age of 20 - had a two-thirds lower risk of developing MS compared with people who had the lowest concentrations. These findings were not replicated in black patients possibly because of lower vitamin D concentrations found in this group and lower numbers of subjects in this arm of the study (*Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis*. Munger KL et al. 2006: *JAMA* 296 (23);2832-2838).

It should be stressed that the studies mentioned here are observational and no large clinical trials have yet taken place using vitamin D as the primary treatment for these conditions. In addition the studies usually find that much higher intakes of vitamin D are required for the protective effect to be realised than is currently the case. Because vitamin D regulates calcium absorption there is a concern that high intake might result in hypercalcaemia. To counteract this great efforts are being made to develop marketable vitamin D analogues which will retain the noncalcaemic benefits without the hypercalcaemic effects. This holy grail is still being pursued.

Apart from those outlined above the list of conditions purported to be associated with low vitamin D concentrations (and conversely to benefit from correcting the deficit) grows apace. The list includes prostate, breast and lung cancer, rheumatoid arthritis, hypertension, skin disorders such as psoriasis, stroke, gingivitis and avoiding tooth loss, and improved lung function.

Finally, the possibility has been raised that factors other than the direct action of vitamin D are responsible for its perceived benefits. For example, increased levels of UV light in more southern latitudes may act in ways other than raising vitamin D. Also, improved calcium homeostasis resulting from increased vitamin D intake may be the primary protective factor. Nevertheless, in vivo and in vitro studies have demonstrated a direct effect of vitamin D on immune and inflammatory systems, the renin-angiotensin system, apoptosis, cellular proliferation, and vascular endothelial growth factor (VEGF) release. The evidence suggests (although circumstantial in some cases), a vital role for the non-calcaemic influence of vitamin D on health and well-being.

-Martin Healy