



## CARDIAC TROPONIN T – A SPECIFIC MARKER FOR MYOCARDIAL DAMAGE

There are 3 components of troponin – C, T and I. Troponin C is common to cardiac and skeletal muscle. On the other hand, there are 3 different isoforms of troponins T and I; they are cardiac muscle, and slow and fast skeletal muscle. Cardiac troponins T and I are specific and are used to detect myocardial damage. They are more sensitive and specific markers for myocardial damage than total creatine kinase (CK) or CKMB.

Cardiac troponin T (cTnT) assays are available at all PathCentre laboratories and the results are used to detect myocardial damage. cTnT is elevated 3-12 hours after the onset of acute myocardial infarction (AMI), peaks between 16 and 24 hours and remains elevated for 5-14 days. The initial increase is due to its release from myocardial cell cytoplasm and the persistent elevation is due to its release from continuing degradation of myofibrils.

cTnT is elevated in 64% of AMI patients presenting to the Emergency Department. Increased cTnT indicates myocardial damage. Since cTnT may remain elevated for 5-14 days after AMI, it cannot be used to detect reperfusion or reinfarction. In these situations total CK is used.

cTnT may be raised in about 30% of patients with unstable angina. Such patients have increased risk of cardiac events. Patients with renal failure may have an increased cTnT. These patients have been reported to have increased frequency of cardiac events.

*(Continued on page 2)*



*Dr Alanah Buck examines one of the mummified heads.*

## FORENSIC ANTHROPOLOGY AT PATHCENTRE

The discipline of Forensic Anthropology has been part of Forensic Pathology at PathCentre for over 20 years.

As a sessional Forensic Anthropologist, Dr Alanah Buck investigates all types of skeletal remains, including those from major crime cases. Dr Buck also assists with detective training for the WA Police Service and liaises with the Department of Indigenous Affairs as an adviser on Aboriginal issues. In addition, Dr Buck is the course controller for the MSc/Grad Dip course for the Forensic Anthropology unit of the Forensic Science course at UWA.

More recently, Dr Buck was appointed as an Honorary Research Associate with the Western Australian Museum and as the Research Director of the Western Australian Museum's Centre for Ancient Egyptian Studies. As a result, Dr Buck has been investigating two mummified

heads around 3000 years old in an effort to establish their age at death and health status. Dr Stephen Knott, Forensic Odontologist, and Dr Buck will carry out facial reconstructions as part of this investigation. Previous work by this pair in conjunction with the WA Maritime Museum, on victims of the Batavia mutiny, has been recounted in a recently published book and a National Geographic television documentary.

With the recent application by Dr Buck as a volunteer for war crimes investigation, the nature of Forensic Anthropology at PathCentre continues to expand.

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In summary, PathCentre recommendations for biochemical investigation of AMI or unstable angina are:

- Request CK and cTnT on presentation.
- If cTnT is raised, the patient has myocardial injury.
- If cTnT not raised, repeat CK and cTnT 6 to 9 hours later. It does not have to be exactly 6 hours after the first sample. If cTnT is still not raised, and there is a high clinical suspicion repeat the cTnT at 12-24 hours.
- For reperfusion and reinfarction, request a total CK.

In chronic renal failure the cTnT may be greater than 0.1 µg/L. If this is the case, repeat the assay at 6 hourly intervals. If there is no further increase in the level, the patient has chronic myocardial damage. However, if there is a further increase in cTnT then the patient has had an acute myocardial infarction.

Finally, it is important to note that raised cTnT indicates myocardial damage of any origin and may be due to myocarditis, severe sepsis, trauma or acute myocardial infarction. Once a positive cTnT is found and the diagnosis of AMI made, there is no justification in requesting another cTnT estimation.

*For further information on the cTnT assay and interpretation of results contact Dr Chotoo Bhagat, Clinical Director, Biochemistry on 9346 2670 or the Duty Biochemist on 9346 3000.*

## DOCTOR'S FORUM IN ESPERANCE

PathCentre recently held a Doctor's Clinical Pathology forum in Esperance. This forum was an excellent opportunity to meet local doctors, discuss clinical issues and technological developments. PathCentre is planning further Doctor's Forums to be held in metropolitan and rural areas in the next few months.

*For further information contact Mrs Terryll Osborne, Marketing Manager on 9346 2142 or e-mail [terryll.osborne@health.wa.gov.au](mailto:terryll.osborne@health.wa.gov.au).*

## PATHCENTRE HOSTS INTERNATIONAL THALASSAEMIA MEETING

A two-day workshop, organised by PathCentre and Queen Mary Hospital, Hong Kong, was held in Perth in March as a collaborative meeting on all aspects of thalassaemia. This meeting was originally designed to be a workshop where countries within our region could get together and discuss mutual problems related to thalassaemia diagnosis, treatment, and counselling. The response was overwhelming and became a full conference with delegates from Australasia, all parts of South-East Asia and North America. Experts from Thailand, Hong Kong, Singapore, Canada and Australia were invited to lecture on a variety of topics. In addition, speakers from Malaysia, Laos, Indonesia, and Cambodia presented data on the current status of thalassaemia in those countries.

Professor Suthat Fucharoen provided an insight into the range of thalassaemia and related haemoglobinopathies, in particular Haemoglobin E, in Thailand where over 12,000 babies are born each year with a major thalassaemic syndrome. This provided some insight into the magnitude of their problem. Reports from other neighbouring countries including Laos and Cambodia, indicated that they face similar issues.

Dr Ivy Ng, the Director of the National Thalassaemia Registry of Singapore, discussed the thorough way in which Singapore has handled the problems of thalassaemia. Despite a carrier rate of 4%, Singapore has successfully reduced the incidence of new thalassaemia major cases to almost zero by a comprehensive strategy of testing, prenatal diagnosis and counselling.

Dr Edmund Ma, University Hong Kong, discussed the importance of recognising compound heterozygotes for both  $\alpha$ - and  $\beta$ -thalassaemia and their significance. Dr Samuel Chong, from Singapore, gave

an impressive account of some of the newer techniques available for identification of thalassaemia mutations. Professor David Chui (Canada) discussed the current status of thalassaemia testing, including prenatal detection. The concept of testing of mother's serum for fetal DNA aroused considerable interest. Australia was also well represented with Drs Joy Ho (NSW) and Andrew Perkins (Vic) giving an insight into the regulation of the  $\beta$  globin gene and the attempt to control the switch from foetal to adult haemoglobin.

### PathCentre and Thalassaemia:

PathCentre as the major diagnostic pathology laboratory for the diagnosis of thalassaemic syndromes in Western Australia, presented 3 years of data for over 700 cases showing the range of disorders seen (48%  $\beta$ -thalassaemia; 40%  $\alpha$ -thalassaemia; 9% haemoglobin S; and 3% others). Testing is performed by a combination of HPLC, haemoglobin electrophoresis and DNA studies for 36 different mutations.

*For further information contact the Duty Haematologist on 9346 2890 or Mr John Prior, Medical Scientist, Haematology on 9346 2903.*

## HEALTH INSURANCE COMMISSION (HIC) BILLING CHANGES FOR PATHCENTRE

The phase-in at PathCentre of standard Medicare billing changes is now complete. Private and non-hospital patients are now asked to supply a Medicare number and signature. This enables PathCentre to directly bill the Health Insurance Commission for pathology testing. This means that patients will have no out-of-pocket payments.

PathCentre has introduced a new A5 combined Pathology Request/ Medicare Assignment to assist in meeting the HIC requirements for billing. These new request forms can be personalised with

the requesting doctor provider details. To order personalised request forms, complete the order form on the insert and fax to 9381 7594.

To access Medicare information two hotlines are available. For general patient Medicare number enquiries call 13 2150. To access Medicare numbers for indigenous people living in rural and remote areas call the Indigenous Access Hotline on 1800 556 955.

## HOMOCYSTEINE UPDATE

Homocysteine is a sulphur amino acid derived from methionine. After a great deal of research, there is now reasonably compelling evidence of an association between plasma homocysteine levels and the risk of vascular disease. The mechanisms by which high homocysteine levels cause disease are not clear. In particular, uncertainty exists as to whether it causes disease or is a product of the disease. Elevated homocysteine levels are a marker of vitamin deficiency, especially folate, and will often respond to folate supplementation. Large-scale prospective clinical trials are underway to determine if folate supplementation reduces the risk of cardiovascular disease.

## Homocysteine Analysis

PathCentre uses an automated immunoassay method for homocysteine analysis. Provided a fasting EDTA plasma is separated from cells within 60 minutes, homocysteine is stable. The PathCentre reference ranges are  $< 13.7 \mu\text{mol/L}$  in men and  $< 11.9 \mu\text{mol/L}$  in women.

## Coronary Artery Disease

There is about a 40% increase in relative risk of coronary artery disease associated with each  $5 \mu\text{mol/L}$  increase in homocysteine concentration. Homocysteine is a better predictor of recurrence of coronary events in patients who have already had an event and also better predicts coronary artery disease in subjects with non-insulin dependent diabetes mellitus compared to non-diabetic patients.

## Stroke

There is a graded increase in the risk of stroke as homocysteine levels rise. Patients with homocysteine concentrations over  $14.4 \mu\text{mol/L}$  have a significantly increased risk of having carotid artery stenosis (odds ratio of 2.0).

## Thrombosis

Homocysteine levels over the reference range predict an increased risk of a first episode of deep vein thrombosis. This effect is stronger in women and is independent of other thrombosis risk factors (protein C, protein S, antithrombin deficiencies and activated protein C resistance) in both sexes.

## Dementias

Elevated homocysteine levels in the elderly are associated with increased risks for Alzheimer's disease. A prospective study reported in the New England Journal of Medicine (2002;346:476-483), showed subjects with a mean age of 76 years and an initial plasma homocysteine level over  $14.0 \mu\text{mol/L}$ , nearly doubled their risk for developing Alzheimer's disease. This effect was independent of other dementia risk factors (age, sex, ApoE genotype, and vitamin levels).

## Pregnancy

Several large clinical trials have established the specific role of folate in the prevention of neural tube defects. The outcome of these studies was the recommendation that all women planning pregnancy should take a vitamin supplement containing folic acid prior to and after conception.

Elevated homocysteine levels have also been associated with a variety of other pregnancy complications including premature delivery, very low birth weight, and placental vasculopathies such as pre-eclampsia and placental abruption. In these women, an elevated plasma homocysteine level may be a marker of folate deficiency that will respond to folate supplementation.

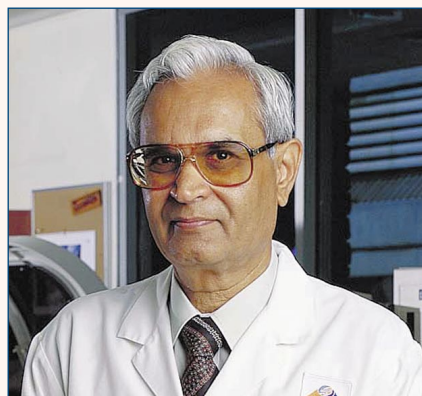
*For further information on the homocysteine assay and interpretation of results contact Dr Ric Rossi, Research Scientist, Biochemistry on 9346 2845 or the Duty Biochemist on 9346 3000.*

## Profile

### DR CHOTOO BHAGAT

Dr Chotoo Bhagat completed his medical degree at University of Natal in Durban, his MSc in physiology at University College, London, and his MD at the University of Natal. He was a senior lecturer in Physiology at the University of Natal before migrating to Australia in 1979. He completed his training in chemical pathology at Sir Charles Gairdner Hospital in 1983. Subsequently he has been a consultant chemical pathologist and since 1995 he has been Clinical Director of Biochemistry at PathCentre.

Dr Bhagat has longstanding interests in



*Dr Chotoo Bhagat, Clinical Director, Biochemistry*

endocrinology, especially the biochemistry of thyroid disorders. He conducts an extensive programme in both undergraduate and postgraduate teaching and takes a special interest in advanced trainees.

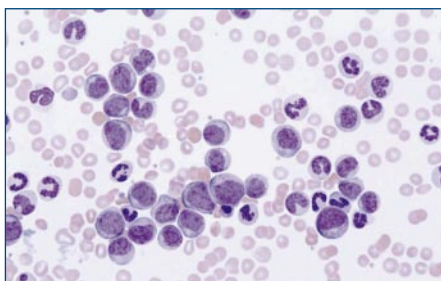
## NEW TARGETED THERAPY FOR MALIGNANCIES

Glivec is a new molecular drug that specifically targets tyrosine kinases. Although initially developed for treatment of chronic myeloid leukaemia, it has also been shown to be effective for other malignancies. In this article Drs David Joske and Greg Sterrett of PathCentre, and Dr Michael Byrne from the Department of Clinical Oncology, Sir Charles Gairdner Hospital describe the role of this drug in chronic myeloid leukaemia and gastrointestinal stromal tumours.

### CHRONIC MYELOID LEUKAEMIA

Chronic myeloid leukaemia (CML) affects 1 in 100,000 Australians, mostly in middle age. It is characterised by a variable chronic phase lasting 1 to 5 years on average, with a marked leucocytosis and splenomegaly. This phase of the disease can be fairly easily controlled. However, the accelerated or "blast crisis" phase is a very refractory and hard to treat form of acute leukaemia.

CML is associated with a chromosomal translocation between chromosomes 9 and 22 resulting in the Philadelphia chromosome. This results in the fusion of *bcr* and *abl* genes and the production of an abnormal tyrosine kinase. This affects cell growth, leading to the development of the leukaemia.



*A blood film of chronic myeloid leukaemia.*

Glivec (imatinib mesylate) is a new drug that kills CML cells containing the *bcr-abl* fusion gene product. This drug produces more responses than standard cells with the Philadelphia chromosome and increased survival for chronic phase disease. Glivec also has some effect in blast crisis though responses are not durable. Glivec has few side effects. In Australia, the supplies of Glivec are limited. Initially Australian patients were included in Phase 3 trials of the drug and in December 2001 it was listed on the PBS, but only for CML in "blast crisis". For newly diagnosed patients and those with chronic phase CML not responding to interferon, Glivec is still not readily available.

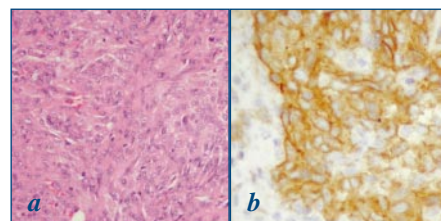
Glivec is a drug designed to block a specific piece of pathogenetic DNA and has successfully done so in clinical practice. Its development augurs a new era of "molecularly-targeted therapy" and we will see many more drugs similarly designed and introduced.

*For further information contact  
Dr David Joske, Haematologist  
on 9346 7600.*

### GASTROINTESTINAL STROMAL TUMOURS (GISTS)

Over the last decade it has become clear that most spindle cell tumours of the stomach and small bowel are not simply leiomyomas or leiomyosarcomas. They probably arise from, or differentiate towards the so-called Interstitial Cell of Cajal (ICC), a part of the autonomic system of the gut, which may be involved in peristalsis ("pacemaker cells"). These tumours are now given the non-committal term "GIST". They may sometimes arise outside the gut or subserosally. Their malignant potential is evaluated by measuring tumour size, mitotic rate and the presence or absence of necrosis or invasion. Tumours larger than 5cm, with >1 mitoses for 10 high power microscope fields, and necrosis, anaplasia and invasion are likely to recur and metastasize. They may show features of neuronal and/or smooth muscle differentiation by immunohistochemistry and electron microscopy. They uniformly express the KIT antigen (CD 117), which is the gene product of the c-kit proto-oncogene. C-kit is a marker of the ICC, and codes for a cell surface receptor growth factor with tyrosine kinase activity. The mutant receptor appears to be active in the absence of the ligand. Glivec was specifically engineered for its anti-tyrosine kinase activity and has been remarkably effective in treating some cases of GIST.

**CASE REPORT:** A 59-year old female presented with a large infra-hepatic GIST. The exact site of origin could not be determined, but the tumour invaded the liver, was 19cm in diameter and showed extensive central necrosis. Tumour recurred 1 year later, with peritoneal and liver metastases.



*GIST: Spindle cell tumour invading liver. (a) H&E staining (b) Prominent membrane staining of tumour cells using antibody to KIT (CD117).*

Chemotherapy with vincristine, adriamycin and cyclophosphamide, and then ifosfamide and etoposide, failed to halt progression. Glivec was commenced and within 1 month the masses had reduced by 50%, both by palpation and by CT scan. The response persists one year later, with the only side-effect being slight peri-orbital oedema. The indolent yet inexorable growth with failure to respond to systemic chemotherapy, are typical features of the natural history of GISTs. The response rate of over 60% to Glivec in those patients with metastatic disease constitutes a quantum leap in therapy for those with this previously intractable condition.

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