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## Calcium Homeostasis

### DR CHARLES APPLETON

### Calcium Homeostasis: A Brief Refresher

Calcium has received much more attention in recent years than previously. With the current heightened interest in vitamin D, many patients are undergoing calcium and PTH investigations following up on abnormal vitamin results. However we are frequently finding unsuspected disorders of calcium homeostasis in the process. For example, we routinely discover one or two new cases of primary hyperparathyroidism each day. This is no longer an uncommon disease.

Calcium circulates in the plasma in two major fractions; ionised and protein-bound, as well as in a number of minor fractions, the most significant of which is the complexed fraction (Fig. A).

#### IONISED (FREE) CALCIUM

The ionised (or free) calcium constitutes around 50% of the total calcium in the normal state and is essentially the only biologically active fraction.

Parathormone (PTH) from the parathyroid glands is largely responsible for control of the circulating level and it does this in a negative feedback loop. If the serum ionised calcium falls, PTH is released from the parathyroids and acts on the gut to enhance calcium absorption (predominantly through activation of vitamin D), on bone to dissolve bone crystal and release calcium and phosphate into the circulation, and on the kidneys to enhance tubular reabsorption of filtered calcium and dumping of phosphate.

Conversely, should the ionised calcium rise for any reason, the PTH secretion will be 'turned off' and the above processes will be reversed.

Parathyroid activity is also modulated by plasma magnesium in a similar fashion although profound hypomagnesaemia (e.g., with cis-platinum therapy) will disable the parathyroid responsiveness, producing a secondary hypoparathyroidism and hypocalcaemia.

It has been recently recognised that a number of **proton-pump inhibitors may cause serious and potentially life-threatening magnesium depletion which presents as an unexplained hypocalcaemia.**



## PROTEIN-BOUND CALCIUM

The protein-bound fraction although biologically inactive, is the source of much of the difficulty in interpretation of serum calcium analyses. This fraction constitutes around 45% of the total calcium and is predominantly associated with albumin. It frequently is responsible for perturbations of the total, while the ionised fraction remains normal.

For example, in conditions in which the serum albumin is low (Fig. B), this fraction and hence the total calcium, will be low but as the ionised calcium is normal, the patient is functionally normocalcaemic. This effect is well-recognised.

This fraction is also responsible for the well-recognised 'tourniquet effect', misleadingly raising the total calcium in difficult venipuncture (Fig. C).

Most laboratories attempt to correct for this by calculating and reporting an 'albumin-adjusted' or 'corrected' calcium using formulae which estimate what the total calcium would have been had the albumin and hence the albumin-bound fraction been normal. These formulae work acceptably with minor variations in serum albumin but the correction becomes progressively spurious as the albumin moves further from the population mean. This is particularly so in patients with renal disease (*vide infra*).

The albumin binding is also pH dependent. In acidotic states, the protein's affinity for calcium declines and the albumin binds less of the total calcium (Fig. D).

Conversely, in alkalotic states (Fig. E), the binding affinity increases and in patients with states of chronic alkalosis (say, post-surgical with protracted vomiting or with naso-gastric suction), this fractional elevation may be sufficient to raise the total calcium to levels exceeding 3.0 mmol/L. However, while the ionised fraction is normal, the patient is functionally normocalcaemic.

The effect of this calcium binding is seen most spectacularly in acute hyperventilation. This produces an acute alkalaemia and the albumin 'steals' calcium from the ionised fraction. The normal homeostasis cannot correct this in the minutes over which it develops, and the patient develops an effective acute hypocalcaemia despite an unchanged total calcium. They present with paraesthesia, tetany and occasionally fitting (all hallmarks of the neuromuscular instability associated with hypocalcaemia) (Fig. F).

## COMPLEXED CALCIUM

The third significant fraction is the complexed calcium. This consists of calcium circulating bound to anions such as phosphate, citrate, etc. and is again biologically inert. It normally constitutes up to 5% of the total. It may become raised with anion retention in renal failure.

As calcium homeostasis is a relatively complex subject, your local Pathologist will be more than happy to discuss cases.

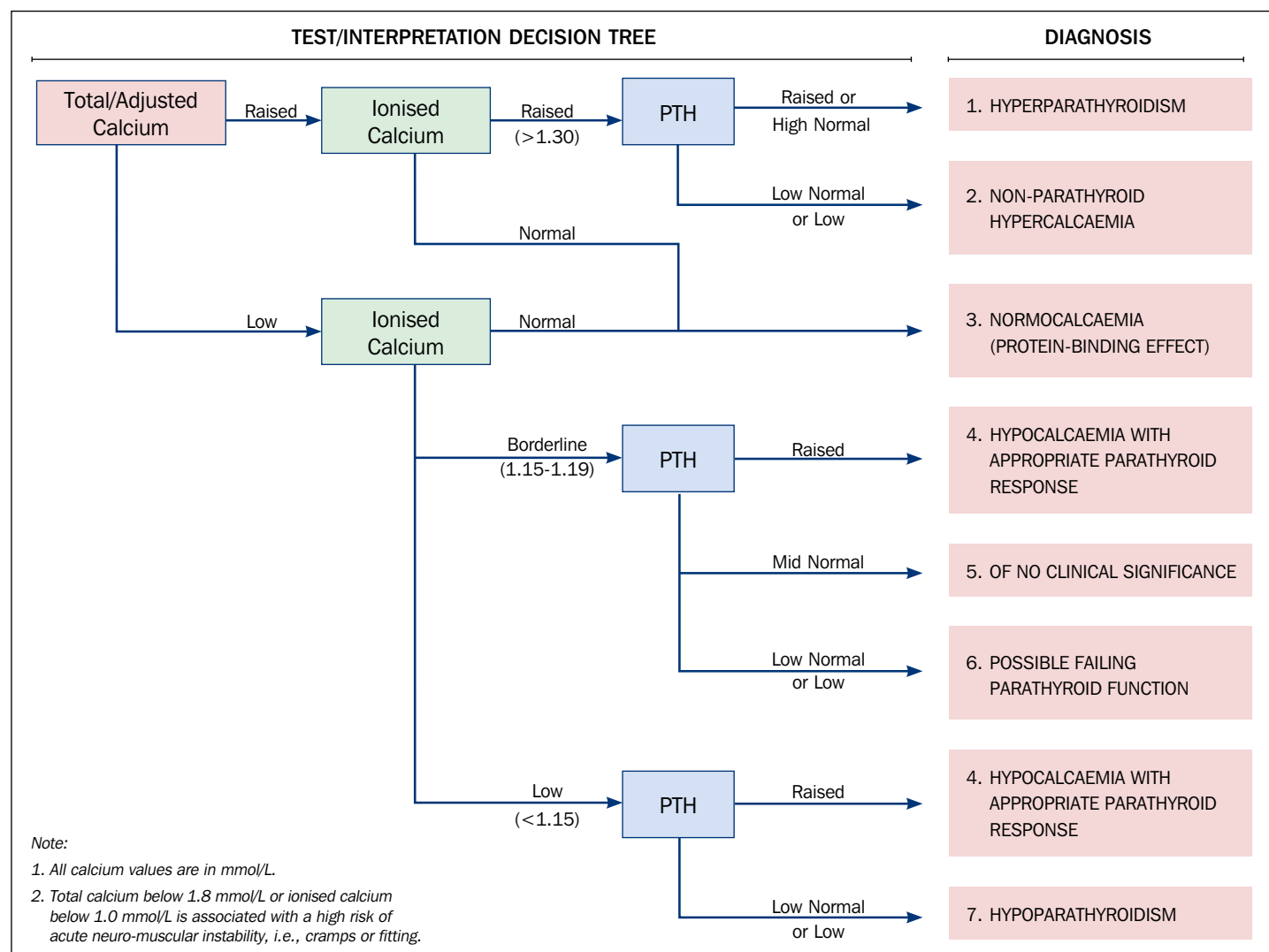
## RENAL FAILURE: A SPECIAL CASE

Calcium homeostasis in renal impairment may be markedly deranged. The accumulation of phosphate raises the complexed fraction by binding and precipitating part of the ionised fraction. The acidosis of uraemia reduces the albumin's affinity for calcium and indeed the serum albumin itself may be low. On the other hand, other proteins such as alpha2-macroglobulin, which bind calcium, may be raised (Fig. G).

All of these tend to render the calcium 'correction' or 'adjustment' formulae invalid and the total serum calcium may be quite misleading. Fortunately, the ionised calcium assay remains valid as it bypasses the above effects and gives a true indication of calcium homeostasis.

Ionised calcium measurement is the mainstay of calcium assessment in renal failure. This is critical as many effects of renal damage (phosphate retention, impairment of renal activation of vitamin D, frequent development of parathyroid autonomy) lead to potentially severe derangements of calcium homeostasis.

# Calcium Homeostasis Disorders: An Approach to Assessment



## Differential Diagnosis

### 1. HYPERPARATHYROIDISM

- Parathyroid adenoma (common - may be part of an inherited Multiple Endocrine Neoplasia syndrome)
- Four-gland parathyroid hyperplasia (seen most often in renal failure)
- Lithium therapy
- Ectopic PTH secretion from non-parathyroid malignancy
- Familial hypocalcuric hypercalcaemia\*

### 2. NON-PARATHYROID HYPERCALCAEMIA

- Malignancy (including multiple myeloma - typically with bone involvement)
- Sarcoidosis (uncommon - follow up testing would include serum ACE and chest x-ray)
- Vitamin D excess (rare except in patients treated for osteoporosis, renal failure (with calcitriol), or overtreated parathyroid failure)
- Vitamin A excess (extremely rare)
- Milk-alkali syndrome (extremely rare)
- Transient effect following marked reduction in level of activity

### 3. NORMOCALCAEMIA WITH UNUSUAL PROTEIN-BINDING EFFECT

- Relatively common, particularly in renal impairment

### 4. HYPOCALCAEMIA WITH APPROPRIATE PARATHYROID RESPONSE

- Vitamin D deficiency (now recognised as relatively common)
- Insufficient dietary calcium (now recognised as relatively common)
- Magnesium deficiency (uncommon unless associated with gastrointestinal disease, cytotoxic therapy or proton-pump therapy)

### 5. 'LOWISH' CALCIUM WITH NORMAL PTH

- Variant of normal

### 6. & 7. FAILING PARATHYROID FUNCTION OR FRANK HYPOPARATHYROIDISM

- After thyroid surgery or irradiation (common)
- Autoimmune endocrine disease (rare but may involve other endocrine glands as well)
- Severe hypomagnesaemia (rare but seen in proton-pump therapy, alcoholism and severe malabsorption)

\* Familial hypocalcuric hypercalcaemia (FHH) is an uncommon, benign inherited form of hypercalcaemia. As it is autosomal dominantly inherited, half of the patient's first degree relatives are likely to be similarly affected. It is important to differentiate it from primary hyperparathyroidism because surgery is not indicated. The differential may be made on the urinary fractional excretion of calcium. Mutation testing is also available but is not Medicare rebatable.

TOTAL CALCIUM

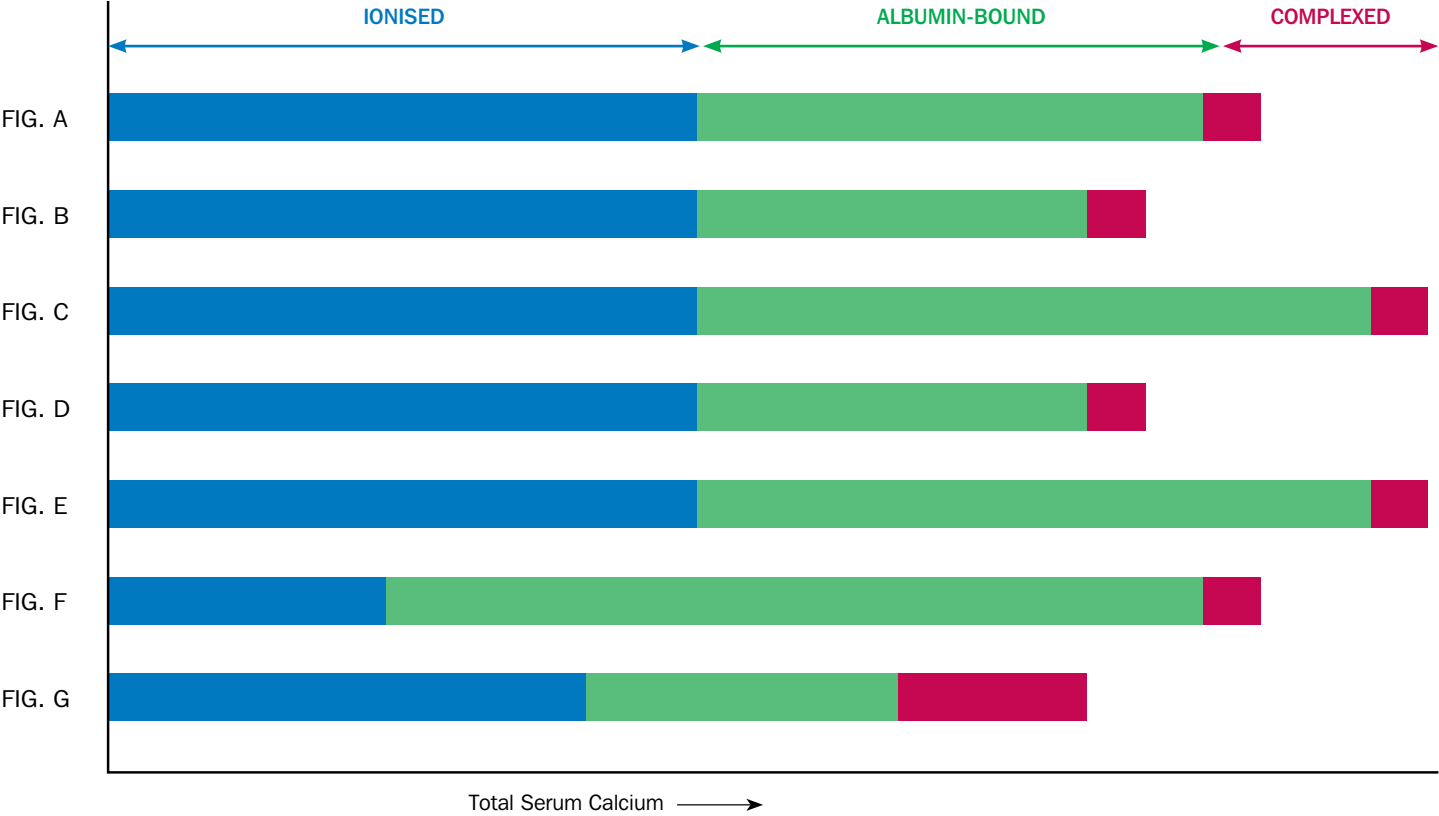


FIG. A	NORMAL	
FIG. B	LOW SERUM ALBUMIN	Normal ionised calcium, Low albumin-bound fraction, Low total calcium
FIG. C	TOURNIQUET EFFECT	Normal ionised calcium, Raised albumin-bound fraction (haemoconcentration), Raised total calcium
FIG. D	CHRONIC ACIDAEMIA	Normal ionised calcium, Low albumin-calcium affinity, Low total calcium
FIG. E	CHRONIC ALKALAEMIA	Normal ionised calcium, Raised albumin-calcium affinity, Raised total calcium
FIG. F	ACUTE RESPIRATORY ALKALOSIS	Raised albumin-calcium affinity, Albumin has 'stolen' ionised calcium, Normal total calcium despite acute 'hypocalcaemia'
FIG. G	RENAL FAILURE	Raised complexed fraction, Low protein-bound fraction**, Ionised calcium may be low or raised depending on parathyroid, vitamin D and phosphate dynamics

\*\* NB - other proteins interfere with albumin correction.

Pathologist Profile

Dr Charles Appleton MMBS (Qld) FRCPA  
PATHOLOGIST IN CHARGE: BIOCHEMISTRY

Dr Charles Appleton graduated from the University of Queensland in 1977 (MBBS), before starting work as a resident medical officer at the Royal Brisbane Hospital in 1978. In 1980, Dr Appleton became a registrar in pathology at RBH, before moving into the role of acting Assistant Chemical Pathologist.

Dr Appleton joined QML Pathology in 1985 as Chemical Pathologist, and was subsequently appointed Partner in Charge of Biochemistry. For part of this time, he worked as Visiting Chemical Pathologist at the Repatriation General Hospital, Greenslopes. In 2003, ownership of QML Pathology changed and his position title was revised to Pathologist in Charge of Biochemistry.

Dr Appleton's special interests include use of computers in pathology result interpretation and reporting, legal aspects of drug testing, inborn errors of metabolism and calcium metabolism.

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Email: Charles.Appleton@qml.com.au



# QML Pathology Updates

## Introducing our New Look Newsletter

Welcome to the first edition of the new QML Pathology Doctors Newsletter. We hope that you will find the new design an improvement and welcome any feedback or suggestions, particularly regarding topics that you would like covered.

If you would prefer to receive the newsletter via email rather than hard copy, please send your details to [info@qml.com.au](mailto:info@qml.com.au) or phone (07) 3121 4506.



## Venesection Bookings

*Changes to venesection bookings in Brisbane, Redcliffe, Ipswich, Toowoomba and surrounding areas only - effective 28 March*

Venesections will only be performed at selected QML Pathology collection centres specialising in the procedure. These are as follows:

- **AUCHENFLOWER** - Suite 90, Fifth Floor  
Sandford Jackson Building, Wesley Hospital, 30 Chasely St  
Phone: (07) 3371 3592  
Bookings available: Monday, Tuesday, Thursday and Friday

- **CAPALABA** - Shop 10, 109 Old Cleveland Rd  
Phone: (07) 3245 4867  
Bookings available: Wednesday
- **NORTH LAKES** - Tenancy 9, Cnr Gregor St West & Winn St  
Phone: (07) 3886 2805  
Bookings available: Wednesday

To make a booking or for further information, please phone the collection centre directly.

## Warfarin Dosing Over the Easter Period

Over the Easter period, the Warfarin Care Clinic will be closed for the registering of new patients. The lines will be closed from 5.00pm, Wednesday, 13 April 2011 and will re-open at 7.00am, Wednesday, 27 April 2011.

During this time it is essential that any new patients on Warfarin are supplied with instructions and/or are referred to their local doctor for supervision. Patients who are currently monitored by QML Pathology and are being discharged from hospital will be accepted over this period.

## Flu Season is Here

CSL Flu Vaccine is available to buy in boxes of 10 and single doses.

Amount	Price (ex. GST)
1 - 50	\$12.50 ea
51 - 100	\$12.00 ea
101 +	\$11.80 ea

To order, please contact QML Pathology Vaccines on (07) 3121 4523 or Fax (07) 3121 4944





# Collection Centre Updates

## NEW COLLECTION CENTRES

### ALDERLEY .....(07) 3352 4181

9 South Pine Rd  
Opening Hours:  
Mon - Fri: 8.00am – 1.00pm

### BEACHMERE .....(07) 5429 0500

Beachmere Village Shopping Centre  
Shop 12, 2 James Rd  
Opening Hours:  
Mon - Fri: 7.00am – 11.00am

### BENOWA.....(07) 5564 7195

210 Ashmore Rd  
Opening Hours:  
Mon - Fri: 8.30am – 1.30pm

### BILOELA.....(07) 4992 1817

Cnr Gladstone & Grevillea Sts  
Opening Hours:  
Mon - Fri: 9.00am – 2.00pm

### BOWEN HILLS .....(07) 3252 7893

8/7 O'Connell Tce  
Opening Hours:  
Mon - Fri: 8.00am – 12.00pm

### BRAY PARK.....(07) 3889 9697

Kensington Village Shopping Centre  
Kensington Way  
Opening Hours:  
Mon & Wed: 8.30am – 12.30pm

### BURANDA .....(07) 3393 1315

Centro Shopping Centre  
264 Ipswich Rd  
Opening Hours:  
Mon - Fri: 8.30am – 1.30pm

### CABOOLTURE .....(07) 5495 3562

Shop 13  
Central Lakes Shopping Centre  
Cnr Pettigrew & McKean Sts  
Opening Hours:  
Mon - Fri: 7.30am – 12.00pm  
1.00pm – 4.00pm

### CLEVELAND.....(07) 3286 5447

177 Bloomfield St  
Opening Hours:  
Mon - Fri: 7.00am – 3.00pm

### COORAN .....(07) 5441 0200

18 King St  
Opening Hours:  
Mon, Wed, Fri: 8.00am – 10.00am

### HIGHGATE HILL.....(07) 3255 2941

40 Gladstone Rd  
Opening Hours:  
Mon - Fri: 7.00am – 12.00pm  
12.30pm – 3.00pm

### IMBIL.....(07) 5441 0200

6 Imbil Island Rd  
Opening Hours:  
Tue: 8.00am – 10.00am

### KAWANA.....(07) 5444 3298

Kawana Shopping World  
Nicklin Way, Buddina  
Opening Hours:  
Mon - Fri: 8.00am – 12.00pm  
12.30pm – 5.30pm  
Sat: 8.00am – 12.00pm

### KAWANA.....(07) 5478 2964

Cnr Kensington Dve and Nicklin Way  
Opening Hours:  
Mon - Fri: 8.00am – 12.00pm  
12.30pm – 4.00pm  
Sat: 8.00am – 12.00pm

### MAROOCHYDORE .....(07) 5479 2639

60 Wises Rd  
Opening Hours:  
Mon - Fri: 8.00am – 12.00pm

### MONTVILLE .....(07) 5441 0200

6/7 168-170 Main St  
Opening Hours:  
Tue & Thu: 8.30am – 10.30am

### PEREGIAN BEACH .....(07) 5471 2080

Unit 6A, 12 Grebe St  
Opening Hours:  
Mon-Fri: 8.00am – 12.00pm

### SANCTUARY COVE .....(07) 5514 8899

Marina Village, Masthead Way  
Opening Hours:  
Mon - Fri: 8.00am – 11.00am

### SPRING HILL .....(07) 3831 0731

Ground Floor, Silverton Place  
101 Wickham Tce  
Opening Hours:  
Mon - Fri: 8.30am – 1.00pm  
1.30pm – 4.00pm

### SPRINGWOOD .....(07) 3290 1501

18 Dennis Rd  
Opening Hours:  
Mon - Fri: 8.00am – 12.30pm  
1.00pm – 4.00pm

### SUNNYBANK .....(07) 3345 3605

Shop 4, 178 Turton St  
Opening Hours:  
Mon - Fri: 8.00am – 12.00pm

### UPPER COOMERA .....(07) 5573 0815

Coomera Village Shopping Centre  
Reserve Rd  
Mon - Fri: 9.00am – 12.00pm

### VICTORIA POINT .....(07) 3870 7149

Shop H – 16B  
Victoria Point Lakeside  
11-11 Bunker Rd  
Opening Hours:  
Mon - Fri: 8.00am – 12.00pm

### WARNER.....(07) 3882 3952

Shop 16  
Warner Village Shopping Centre  
Cnr Samsonvale & Old North Rds  
Opening Hours:  
Mon - Fri: 8.00am – 1.00pm

# Doctor's Noticeboard



## DR NAMRATA BAJRA

Phone: (07) 3871 3317

Fax: (07) 3232 7585

Suite 30, Level 2  
Wesley Medical Centre  
40 Chasely St  
Auchenflower

Dr Namrata Bajra, Obstetrician and Gynaecologist, has recently started her practice at the Wesley Medical Centre with special interest in high risk obstetrics, colposcopy, complex pelvic surgery and laparoscopic surgery.

Dr Bajra also consults from Carindale Specialist Centre (located within Westfield Carindale) once a week, and is available at any time to discuss patient management and answer any questions regarding patient care.



## DR ANDY STAMATIOU

Obstetrics, Gynaecology  
and Fertility

Phone: (07) 3613 9774

Dr Stamatiou's practice includes the management of pregnancy and labour, as well as the management of high risk pregnancy, and all general gynaecological conditions including menstrual disturbances, menopausal conditions, endometriosis, fibroids, prolapse and incontinence. Surgical procedures are mainly vaginal and laparoscopic, with Dr Stamatiou having a special interest in the latter.

Dr Stamatiou's rooms are located at Suite 5, Level 7, Brisbane Private Specialist Centre, 259 Wickham Tce, Spring Hill. He also has a weekly clinic at The Hub, 2 Rickey St, Capalaba, and a part time public post at the Redland Hospital. For all appointments and enquiries, please phone (07) 3613 9774.

**DR NICHOLAS BOYNE**, Vascular and Endovascular Surgeon, is based at the Wesley Hospital in the Sandford Jackson Building, and also has a public appointment at the Royal Brisbane and Women's Hospital.

In addition Dr Boyne has commenced consulting at:

- **Bywater Medical Specialist Centre**  
169 Seventeen Mile Rocks Rd, Oxley
- **Logan Specialist Centre**  
Springwood Plaza  
3 Dennis Rd, Springwood.

Areas of special interest include vascular and endovascular surgery, aortic and carotid surgery, peripheral vascular disease and varicose veins.

### ALL REFERRALS AND APPOINTMENTS:

Phone: (07) 3720 9261

Fax: (07) 3720 8848

Suite 88, Level 5  
Sandford Jackson Building  
30 Chasely St, Auchenflower

**DR DEL HINCKLEY**, Plastic and Reconstructive Surgeon, advises that her private practice in plastic and reconstructive surgery closed in December 2010. She will continue to work in public practice at the Royal Brisbane Hospital.

Dr Hinckley would like to thank all doctors, and nursing and paramedical staff for their support and assistance since 1977.

From January 2011, Dr Hinckley may be contacted by email at [stedel@bigpond.com](mailto:stedel@bigpond.com).

**DR NEIL SHILTON**, Obstetrician and Gynaecologist, wishes to advise that he is retiring as of 21 April 2011.

Phone: (07) 3216 9011

Fax: (07) 3216 9022

Suite 213 B, Times Square  
250 McCullough St, Sunnybank

# Infectious Diseases Report

GEOGRAPHIC DISTRIBUTION - JANUARY 2011

ORGANISM	Regions (as per key below)															TOTAL			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	JAN	DEC	OCT	NOV
Adenovirus (not typed)	2	10	2				11		1		8	3		3	1	41	49	37	15
Adenovirus (typing pending)	1	2	1							1	1					6	8	18	11
Barmah Forest virus	2	7	2				4		7	7	5	8	1			43	32	25	9
Bordetella pertussis	3	39	16	3	1		27		57	15	71	47	12	6	9	303	290	351	190
Brucella species	1		1							1	1			1		5	4	1	3
Campylobacter jejuni																0	0	0	0
Chlamydia pneumoniae																0	0	0	0
Chlamydia trachomatis, not typed	78	109	34	19	2		61		45	16	146	44	13	40	14	621	623	755	348
Coxiella burnetii		1	1								1	2	2	2		9	9	5	2
Cryptococcus species																0	2	3	2
Cytomegalovirus (CMV)	2	13	5	2			6		5		9	4	2	4	3	55	55	71	37
Entamoeba histolytica																0	0	0	0
Enterovirus - not typed																0	0	1	0
Epstein-Barr virus (EBV)	9	24	3	3			15		20	1	24	15	4	5	6	129	100	145	77
Flavivirus unspecified	4	2	1				3		1			4		1		16	16	21	7
Hepatitis A virus				1												1	4	5	3
Hepatitis B virus	2	11	1				13		1	1	31	1	1	3		65	59	86	50
Hepatitis C virus	14	40	8	3		1	23		17	8	53	23	10	6	4	210	222	304	149
Hepatitis D virus																0	0	0	0
Hepatitis E virus							1									1	1	0	1
Herpes simplex Type 1	15	50	18	9			49	1	31	8	76	20	8	9	10	304	242	297	159
Herpes simplex Type 2	10	35	4	3			18		19	1	30	19	5	3	1	148	141	201	116
Herpes simplex virus - not typed																0	0	0	0
HIV-1										1	1		1			3	7	10	2
HTLV-1																0	0	0	0
Influenza A virus	7	3			1	1	8		3	4	9	6		5	1	48	48	46	43
Influenza B virus	1	1							1		1	4				8	7	18	9
Legionella pneumophila (all serogroups)		1								1	3					5	0	1	0
Legionella species											2			1	2	5	2	3	1
Leptospira species	3						1			1	1	1	1			8	1	2	5
Measles virus																0	2	1	0
Mumps virus												1				1	0	0	1
Mycoplasma pneumoniae	1	6	1	2		2	3		3	1	7	2	1	1	1	31	13	18	8
Neisseria gonorrhoeae	9	4	1	1	1		9			1	7			2		35	51	40	28
Parainfluenza virus Type 1																0	0	0	1
Parainfluenza virus Type 2			1			1										2	2	3	0
Parainfluenza virus Type 3	1	3					2		1		1	1	1	1		11	30	77	27
Parvovirus		1	3				3		3			3				13	12	8	8
Pneumocystis carinii		2														2	2	1	1
Respiratory Syncytial virus		3	2	1			5		6	1	3	2		8		31	26	27	17
Rickettsia - Spotted Fever Group			1	1					1				1		1	5	9	7	3
Ross River virus	4	3	4				5		7	6	5	3	1	10	2	50	31	33	14
Rubella virus																0	0	0	1
Salmonella paratyphi A																0	0	0	0
Salmonella paratyphi B																0	0	0	0
Salmonella typhi																0	0	0	0
Shigella dysenteriae																0	0	0	0
Shigella flexneri																0	0	0	0
Streptococcus Group A	6	13	8	2			8		4	6	7	9	3	7	1	74	66	80	38
Toxoplasma gondii							1									1	0	2	0
Treponema pallidum	19	10	4				20		8	5	26	4	8	8		112	84	116	62
Trichomonas vaginalis	10	2	1				1				1			3		18	19	15	8
Varicella Zoster virus	8	30	12	2			35		13	4	43	24	4	6	4	185	175	204	124
Yersinia enterocolitica																0	0	0	0
<b>TOTAL</b>	<b>212</b>	<b>422</b>	<b>135</b>	<b>52</b>	<b>5</b>	<b>5</b>	<b>332</b>	<b>1</b>	<b>254</b>	<b>90</b>	<b>573</b>	<b>250</b>	<b>79</b>	<b>135</b>	<b>60</b>	<b>2605</b>	<b>2444</b>	<b>3038</b>	<b>1580</b>

## REGIONS:

1 Cairns  
2 Gold Coast/Northern Rivers  
3 Ipswich

4 Mackay  
5 Mount Isa  
6 New England  
7 North Brisbane Suburbs

8 Northern Territory  
9 Redcliffe  
10 Rockhampton  
11 South Brisbane Suburbs

12 Sunshine Coast  
13 Toowoomba  
14 Townsville  
15 Wide Bay/Burnett

DECEMBER 2010 AND FURTHER HISTORICAL CLINICAL DATA CAN BE OBTAINED BY CONTACTING YOUR LOCAL MEDICAL LIAISON OFFICER.

