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HAEMATOLOGY UPDATE
A difficult diagnosis of acute leukaemia in a 13-month-old infant

SAAL FOLEY LECTURE
"A healthier future for all Australians" Integrating laboratory medicine into the vision

ORIGINAL ARTICLE
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“A healthier future for all Australians”

Integrating laboratory medicine into the vision

Vincent Williams

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Transcript of the lecture presented at the AACB AIMS Combined Scientific Meeting 2010, Perth WA

Introduction

This paper is an account of the Saal Foley address that was delivered at the combined Australian Institute of Medical Scientists / Australasian Association of Clinical Biochemists (AIMS/AACB) Annual Scientific Meeting held in Perth in November 2010. The information presented here is similar to the original delivery with appropriate references for the reader who wishes to pursue specific issues and also to promote discussion among the readership of important matters that impact our profession.

The Saal Foley Lecture honours two former presidents of AIMS namely John Saal and John Foley. These men contributed significantly to the education of medical scientists and both were instrumental in progressing the academic standing of the medical scientist qualification from a certificate course taught in technical college night schools to an accredited bachelors degree with postgraduate opportunities at universities around Australia.

The topic of this presentation was inspired by the underlying themes of the AIMS AACB Meeting namely, global disease, harnessing technology, quality delivery and ensuring better patient outcomes – issues that dovetailed into dynamic events that are currently shaping the Australian health system. The title also draws on one of one of the many reports recently tabled by the federal government of Australia that highlight the health reforms that will assist the future health of Australians (NHHRC 2009). The demands being made on the health system by changes to Australia’s population have placed increasing pressure on health delivery that has not been matched by provision of facilities with sufficient capacity or staff in sufficient numbers to meet growing needs. Recently significant attention has been given by the Australian government to the provision of increased numbers of medical practitioners and nurses, but we know the success of much of their work depends on quality pathology testing. While the profile of the pathology industry is not as public as other allied health professions the vital contribution it makes to patient management demands that its workforce and funding should to be considered as part of any broader health reform plan.

This presentation will examine some of the main drivers of health reform in Australia and explore some of the issues facing the pathology workforce and how it might respond to maintain a strong presence among other health professionals. The solutions may include changes to the role of medical scientists that John Saal and John Foley may never have envisaged.

What is driving the Australian health reforms?

While responsibility for health in Australia is shared by state and federal governments, in 2010, two alternative blueprints for the future management of Australia’s health were proposed by successive prime ministers. The tabled reforms would deal with public health management at a national level and be driven by myriad issues including population demographics, emerging chronic diseases growing disquiet in the Australian community over access to medical care, personal tragedies resulting from health system failure and the health workforce.

Australia’s population is changing

Australia’s population is growing at a rate not seen since the 1970’s (IGR 2010). The Australian Bureau of Statistics reported that in October 2010 there were more than 22 million Australians and unlike many countries in the world, the population showed a positive growth trend (Table 1) (ABS 2010).
There has been considerable public debate over the future growth of Australia’s population and the social and environmental consequences of a “big” Australia. Population projections suggest that growth is inevitable and steep spikes in immigrant numbers in recent years have been contributed to by political unrest in many parts of the world and the minerals boom. When this feature is combined with the observed rising fertility rate a population of 35 million is predicted for 2056.

Table 1. Australia’s estimated population growth rate (Modified from ABS 2010)

<table>
<thead>
<tr>
<th></th>
<th>Population October 2010</th>
<th>One Birth</th>
<th>One Death</th>
<th>International Migration</th>
<th>Net Increase-on person per 1 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22,630,265</td>
<td>1min 47 sec</td>
<td>3min 44 sec</td>
<td>1min 54 sec</td>
<td>1 min 13 sec</td>
</tr>
</tbody>
</table>

The increased number of people will place considerable pressure on the entire resources Australians draw on in addition to health.

Table 2. Population projections for Australia 2006-2101 (modified from ABS 2009)

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Fertility rate-babies per woman</th>
<th>Net overseas migration-persons</th>
<th>2056 million</th>
<th>2101 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series A</td>
<td>2.0</td>
<td>220,000</td>
<td>42.5</td>
<td>62.2</td>
</tr>
<tr>
<td>Series B</td>
<td>1.8</td>
<td>180,000</td>
<td>35.5</td>
<td>44.7</td>
</tr>
<tr>
<td>Series C</td>
<td>1.6</td>
<td>140,000</td>
<td>30.9</td>
<td>33.7</td>
</tr>
</tbody>
</table>

Australians now enjoy the third highest life expectancy in the world behind that of Japan and Switzerland and the number and proportion of older persons has also grown considerably (Table 3) (AIHW 2010a). Numbers of Australians aged 65 or more have increased dramatically while the rise in the number and proportion of people aged above 85 has increased even faster (Table 4) (AIHW 2009). In 1970 Australia had 184 individuals aged 100 years; in 2006 census data showed 3,154 and 41% were still living independently. By 2020 it is anticipated that there will be in the order of 12,000 centenarians (Richmond 2008).

Table 3. Life expectancy estimates (years) for selected countries, by sex, 2005-2010 (modified from AIHW 2010a)

<table>
<thead>
<tr>
<th>Country</th>
<th>Male</th>
<th>Country</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iceland</td>
<td>80</td>
<td>Japan</td>
<td>86</td>
</tr>
<tr>
<td>Japan</td>
<td>79</td>
<td>Hong Kong</td>
<td>85</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>79</td>
<td>Australia</td>
<td>84</td>
</tr>
<tr>
<td>Australia</td>
<td>79</td>
<td>Switzerland</td>
<td>84</td>
</tr>
<tr>
<td>Switzerland</td>
<td>79</td>
<td>Spain</td>
<td>84</td>
</tr>
<tr>
<td>Sweden</td>
<td>79</td>
<td>France</td>
<td>84</td>
</tr>
</tbody>
</table>

While the media portrays the aged as forgetful, feeble and stubborn this is probably an incorrect stereotype; the aged population is not homogeneously unwell and we are seeing more frequent images of the elderly living independently and productively.

Age however brings with it an increasing likelihood for the need to access the health service at general practitioner (GP), allied health, hospital or aged care levels. The demand on the health system is compounded by health issues resulting from lifestyle choice and the high value placed on health care and access to it by the community.

Emerging chronic diseases

Australia is a country of social contrasts with great wealth and abject poverty in the community and these characteristics contribute to the rising prevalence of the chronic disease related to affluence and neglect including cardiovascular disease (CVD), diabetes and many types of cancer.

Chronic diseases are characterised by complex causality, long latency periods, a prolonged course of illness and functional impairment or disability (AIHW 2010b). Those features cover a broad range of conditions that occur in all age groups from short sightedness through to malignant disease but each has a level of impact on the health system. Based on recent figures, most Australians (75%) have a chronic health issue that are collectively responsible for 80% of the burden of disease and injury in Australia, account for 70% of health expenditure, are part of 50% of all GP consultations and are the leading causes of disability, loss of productivity and death in Australia. The proportion and number of chronic conditions increases with age (Table 5) (AIHW 2009). Most of the total burden of disease however is attributable to a small number of causes (Table 6) (AIHW 2010b). All cancers combined (19% of the total), CVD 16% and mental disorders are the leading broad cause of disease burden. Within 10-15 years type 2 diabetes is predicted to become the leading cause of chronic disease. The prevalence of that condition in 2010 is 3.6% (approximately 700,000 cases) with the prediction that it will increase to 9% (2.1 million) by 2023.
Impact of chronic diseases on health services

The Australian community places a high value on health care but there is growing disquiet over the availability of and access to medical care and treatment. This applies not only to rural and regional Australia but to city based communities that have difficulty accessing a GP. Consequently the popular press regularly presents reports of the overuse of emergency departments (EDs) that leave our public hospital facilities staggering under large numbers of patient episodes and non-essential admissions. For example seven million patients were seen at ED centres in Australia in 2008-9 compared with 6 million patients seen in 2004-05. Over the same time period hospital admissions were high at five million in 2008-9 compared with four million in 2004. More than half of all potentially preventable hospitalisations were from selected chronic conditions (AIHW 2010c). The result of the increased demand for services has been diversion of essential resources placing limits on the completion of more complex treatment, reduction of elective surgery opportunities, exposure of staff to increased potential for errors and placing the safe performance of many processes at risk. This has also contributed to the unacceptable level of personal tragedies resulting from system failure. There has been considerable publicity over the failure of the health system governance in regulating the credentials of health practitioners, adverse reactions to mass immunisation and much concern by the time taken by state and federal authorities to respond to such failures.

Cost of health

Australia’s spending on health is similar to other developed nations and expenditure in 2007–08 equalled 9.1% ($103 b) of gross domestic product (GDP).

As a share of its GDP, Australia spent more than the United Kingdom in 2007–08 (8.4%), a similar amount to the OECD median (8.9%) and much less than the United States (16%). State and federal governments funded almost 70% of health expenditure in 2007–08 with the remainder coming from private health funds and direct payment by patients (AIHW 2010b).

The level of expenditure has significant implications for future funding as the number of taxpaying workers per retiree will change dramatically within the next 20 years. The boost to the tax base to cover health will have to be drawn from other sectors and call for innovative legislation such as the minerals resources tax, carbon tax and increasing the retirement age. Improving the general health of Australians is another cost reduction strategy.

Promoting healthy living - preventative reforms

Lifestyle risk factors contribute to an estimated 30% of the disease, death and disability burden. In Australia in 2007-08, 61% of adults and 25% of children aged 5 to 17 were overweight or obese. Smoking is still the single most preventable cause of ill health and death in Australia although compared to other OECD countries Australia’s rate of smoking is lower. In 2007, only 5% of 14-16 year olds consumed the recommended intake of vegetables; among young the incidences of sexually transmitted infections (STI) was at epidemic proportions and less than half of the population had adequate level of health literacy (AIHW 2010b).

The government has recognised that much of the chronic disease burden is related to behavioural causes and biomedical outcomes. It believes alterations to unhealthy lifestyle can be targeted through education programmes and chronic conditions should be managed in the community away from EDs to help relieve public hospital pressure.

National Preventative Taskforce

In May 2010, the National Preventative Health Taskforce declared its intention to improve the overall health and wellbeing of the population through added support of existing policies that aimed to reduce the overall burden of disease and disability on the Australian community (NPT 2010) The reforms aim to “embed prevention and early intervention into every aspect of our health system and our lives”. The three levels of care that define the programme are

- Primary care: to prevent movement of the “well” to the “at risk” through promotion of health and the prevention of illness
- Secondary care: to prevent the “at risk” progressing to “established disease” via early detection and prompt intervention e.g. screening Pap smears, mammograms, occult blood testing.

### Table 5. Proportion (%) of chronic conditions reported by age 2004-05 (modified from AIHW 2010b)

<table>
<thead>
<tr>
<th>Number of chronic conditions</th>
<th>Age group 5-64</th>
<th>Age group 65 plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>47</td>
<td>18.4</td>
</tr>
<tr>
<td>One</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Two</td>
<td>14</td>
<td>26.7</td>
</tr>
<tr>
<td>Three</td>
<td>5.1</td>
<td>15.3</td>
</tr>
<tr>
<td>Four</td>
<td>14</td>
<td>5.0</td>
</tr>
<tr>
<td>Five or more</td>
<td>0.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

### Table 6. The leading causes of chronic disease in Australia (AIHW 2010b)

1. Cardiovascular disease
2. Depression
3. Type 2 diabetes
4. Dementia
5. Stroke
6. Lung cancer
7. COPD
8. Adult onset hearing loss
9. Colorectal cancer
10. Asthma
• Tertiary care: to increase the number of healthy older Australians, to prevent or delay progression and complication from disease and promote adjustment to chronic conditions.

The intention is to move primary and secondary and where possible tertiary care back to the community to reduce the burden in hospitals and EDs.

Preventative reforms - January 2011

The government believes that for too long Australians have clung to the idea that the nation’s health depends primarily on hospitals for emergency care and surgery. It is also the government’s view that most essential healthcare can be delivered outside the hospital in community general practices and specialist clinics and changes to support this approach have been established.

Changes to funding arrangements for medical services since 2003 have encouraged more GPs back to the workforce and further federal support has been made available for GPs to manage chronic disease. These include incentives for targeting specific conditions such as cardiovascular disease, diabetes, wellness checks for specific age groups and funding for the appointment of practice nurses to assist in primary care delivery. Improving access of the community to 24 hour GP services and integrated healthcare is planned with the building of GP super clinics and Medicare locals.

Media campaigns targeting the risks of tobacco smoking, excessive alcohol consumption, illicit drugs, the importance of good nutrition and the benefits of regular exercise have commenced with a view to stimulate the public consciousness to consider the benefits of healthier life choices.

To achieve these goals there has been considerable effort by the government to provide more health professionals to deliver the quality safe care and this is the final driver of health reform considered here.

The Australian health workforce

At the present time, approximately 600,000 Australians are employed in health service occupations representing approximately 6% of the national workforce. This broadly comprises 234,000 nurses, 60,000 medical practitioners, 54,000 allied health professionals and 245,000 “others” that includes medical scientists among many other smaller contributing groups (NHHN 2010). In 2009 The National Health Workforce Taskforce reported on the projected demands for the health workforce supply based on population growth, aging and predicted demand by increases in community illness at all ages (NHWT 2009). For the purpose of that report the allied health professions were represented by those groups that could provide workforce statistics drawn from national registration or accreditation data therefore the medical scientists workforce was not included. The project showed an overall shortfall of health practitioners at a macroscopic level in most professional groups. It concluded that increases in student numbers could not be the only way to meet demand and other approaches such as increased international recruitment, improving retention rates of practitioners, and workforce reform would also need to form part of any national and jurisdictional response. This report and other data prompted the funding of workforce initiatives by the federal government to help ensure that Australians in city and regions might be able to access healthcare.

Federal Health Workforce Plan

The government has embarked on a 10 year plan to improve access to primary health care and is assigning considerable funding for the training of more medical practitioners for general practice and other specialist areas in addition to substantial international recruiting (NHHN 2010). Funding has been allocated to increase university places for medical students to help to address the current and anticipated shortfalls. Funding has been made available to medical practices to assist with the appointment of nurse practitioners who have been granted increased authority to request Medicare funded pathology tests related to wellness investigations and other primary care procedures. In this way the traditional gateway to healthcare for the community will be enhanced. Funding has also been allocated to provide allied health professionals placements in areas of need. In summary in 10 years the reforms will:

• Increase the number of GPs by 5,500 and specialist physicians by 648 at a cost of $632 million
• Support nurse positions in general practice at a cost of $390.3 million
• Support 1000 clinical training scholarships for allied health professionals in rural locations – cost -$6 million

This action will have a strong downstream effect on pathology providers.

The increasing demand for pathology

It is acknowledged that pathology testing by GPs is the mainstay of preventative health and the early detection of disease in the Australian health system. It is fundamental to clinical diagnosis and management decisions and government policy is profoundly influencing the volume of testing undertaken by GPs (AAPP 2008).

With more GPs in the workplace seeing older and sicker patients, pathology providers are performing more tests for chronic disease and preventative health investigation.

Figures for the number of pathology services recorded by Medicare reflect a steady increase in patient
services e.g. for the year 2000-01 there were 62 million services compared with 87.5 million in 2006-07 and 100.5 million in 2008-09 (DOHA 2010b). These figures represent the number of tests for which a benefit was paid and does not reflect the tests performed by laboratories and not charged due to exclusion by the coning rule that only permits laboratories to bill Medicare for three tests per patient episode.

The demand for pathology has also been due to facilities being readily accessible and testing being highly affordable. The pathology industry has the highest bulk billing rate of all health services and it is stringently regulated internally and externally ensuring quality and safety. Thus pathology laboratories have the confidence of GPs and the community has an expectation of the ready availability of a pathology collection centre, little or no charge and timely result turnaround. For those of us looking out from the laboratory this has made the pathology test an undervalued commodity.

**Pathology business is under pressure**

Despite the contribution of pathology testing to the health of Australians the federal government has delivered little in the way of positive changes to funding criteria that might have improved their revenue stream.

The 2009-10 Federal Budget reduced funding of specific pathology services resulting in an estimated 7% loss of revenue. Another government initiative in 2010 was removing restrictions on laboratory specimen collection centres (HIA 2010). In the first two weeks following the lifting of those restrictions 500 new collection centres were approved for opening around Australia as laboratories tried to maintain market position (The Australian August 2nd 2010).

In 2011 patients will receive their pathology requests on a generic form that will allow them to choose any provider for their testing further blurring the ability of pathology providers to predict income.

In this environment the focus of laboratory operations has understandably been on financial matters and quality while succession planning of staffing has been poorly managed.

Pathology testing might be the mainstay of clinical decision making but in many settings increased volumes of work have ensured the wheels of pathology keep turning ever faster and for those who have been in the industry for more than 20 years the rising tide of pressure has permanently altered the operational characteristics and culture of pathology laboratory service.

**Pathology workforce issues**

A comprehensive national census of the pathology workforce has never been undertaken but at this time there are at least two large surveys of the pathology workforce initiated by the Department of Health and Aging that are planned or approaching completion. The snapshot of the NPAAC workforce report in 2007 revealed that there is a shortage of skilled pathologists and scientists in Australia (NPAAC 2007). It predicted that within the next decade a significant number of retirements of both scientists and pathologists will have considerable impact on the skills base in the profession.

The Royal College of Pathologists of Australasia (RCPA) has addressed this to some extent by the introduction of government supported training programmes for pathology registrars however in most laboratory workplaces there has been no formal succession planning for Senior Scientists. The medical scientist profession now faces the prospect that the future number and capacity of the workforce will be insufficient to maintain the current quality level let alone meet increased demand for services. The NPAAC survey was conducted to obtain an estimate of laboratory supervision capacity. It showed that in 2007 more than 50% of the Senior Scientists in the survey were 50 year of age or older (Fig 1). This information is now almost 5 years old and a number of participants will already be retired. It is clear from that data there will be a serious shortfall of skilled Senior Scientists in the near future. The loss of expertise is a cause for concern especially in the context of capacity to support the quality of care at existing levels and the increased demand for services.

That survey also projected demand for scientists in numbers sufficient to sustain the workforce to the year 2032 (Fig 2). The numbers required would compensate for the predicted loss to the workforce by retirees to the year 2017 and growth in the industry of 3% or 5% per year. The enrolment of trainees required to sustain the workforce would have had to increase by 50% (from 2007) and be maintained at that number each year to satisfy future demand. Those projections also implied that the trainees
recruited would stay on in the profession. This was a relatively small study and at this time we do not have a clear national picture for pathology workforce requirements.

**Figure 2:** Projected demand for trainee scientists to 2032. (reproduced with permission NPAAC 2007)

It may be relevant to see what is occurring in USA where solid statistics are available for laboratory scientists and the population demographics are not dissimilar to Australia. The approaching shortage of laboratory personnel there is acknowledged by the following facts:

- Hiring difficulty has been reported by 44% of laboratories
- An estimated 150,000 new technologists will be needed by 2014 through a combination of 81,000 retiree replacements and 68,000 new positions due to growth in the industry
- There has been a 67% drop in graduates since 1977 e.g. 6519 in 1977 down to -2141 in 2005
- The workforce is mature and aging with 40% of current workforce likely to retire in 10 years and the average age of current scientist in the workforce is 49.2 years (CAAHEP 2008).

The solutions to this problem in Australia will require urgent action at a number of levels including secondary and tertiary education centres, within the industry and by the professional body.

**Can we avoid a scientist shortage?**

There are eight universities in Australia that offer AIMS accredited bachelor degree courses in laboratory medicine. Approximately 240 graduates are available to enter the profession per year (Legge and Assoc., 2008). A proportion of those are international students who return to their country of origin. There are no records kept by universities on their students’ progress after graduation and as the medical scientist is not required to register to practice there is uncertainty around supply, demand and movement of graduates.

The range of courses, science based and other, now offered by universities means there is increased competition between faculties for students of sufficient academic standing to enter study programmes offered by their schools. Furthermore, graduate entry programs in medicine, pharmacy and physiotherapy appeal to laboratory medicine graduates wanting to pursue careers that offer different career opportunities. Across the tertiary science education sector universities have great difficulty attracting appropriately qualified personnel to fill academic vacancies (The Australian May 26 2010). This applies to Schools of Biomedical Science where the lack of experienced staff is resulting in the niche subjects such as cytology and immunology being dropped from curricula at some universities.

Scientists who enter industry may choose to leave the profession for alternative careers if skills and experience are unrewarded. The lure of high paying appointments outside of the profession with better long term opportunities has become a feature in our resource driven economy and affects the retention of trained personnel in many sectors.

The rigours of unsociable hours that are now part of the operational landscape of pathology laboratories and the desire by many scientists for a work-life balance has seen an increase in the number choosing to work part time appointments.

It is also very discouraging for graduates to find that the only position they might attain after four years of university (undertaken at significant personal cost) is at laboratory assistant level. High turnover of staff does little to instil confidence in the work group and delivers the wrong career message to graduates entering the workplace. These are workplace issues that operations managers of laboratories have to deal with particularly when trying to strike a balance between business overheads and market expectations.

The financial constraints on the operation of laboratories may ultimately result in the industry being dominated by only the largest companies. The impact of deregulation may be the death knell for smaller private laboratories that are unable to secure a viable market share.

The situation has meant that alternative methods of operating health delivery need to be considered to maintain efficiencies.

**New technology and processes will assist pathology workload management**

Pathology testing is a dynamic process that changes constantly as new investigations emerge and alternative methodologies are adopted. There are few industries
that adapt or develop new technology as vigorously as the pathology industry. The operational environment also places pressure on laboratories to continue to improve productivity and provides the catalyst for innovation. In my experience however when any new technology is accepted into the workplace it invariably adds another level of complexity and opportunity for scientist specialisation. For example point of care testing (PoCT) is a sensible innovation in selected areas. It is a result of the demands placed on EDs, intensive care wards and outpatient clinics that some pathology testing has moved outside of the laboratory. PoCT is highly applicable to the primary care activities of GPs taking on chronic disease management and has obvious advantages in rural and remote settings. It creates an opportunity for the laboratory to extend its traditional service to training, competence checking, quality control and maintenance to ensure patient safety is assured.

Improved automation in many facets of laboratory medicine including clinical biochemistry, haematology, microbiology and anatomical pathology has assisted in management of burgeoning workloads.

Molecular pathology testing is increasing in importance in diagnosis and patient management. The impact of genomics and proteomics is only beginning to be realised. Discovery of susceptibility genes has fueled expectations about the opportunities of genetic profiling for personalised medicine. Information from genome wide association studies may ultimately alter many aspects of clinical practice and health care. The anticipated predictive power of this science may permit earlier and more accurate diagnosis of common conditions and allow appropriate interventions.

At a fundamental operational level both government and the industry recognise that request management strategies will be important to assist in reduction of unnecessary testing as increasing numbers of GPs enter the workforce. This will require a range of actions including continuing education of GPs, decision support of laboratory testing by pathology providers, test request modules and rationing strategies (DOHA 2010a).

Pathology workforce challenges and priority actions

What must our profession do then to firstly, attract students to laboratory medicine courses at universities and secondly, ensure opportunities are available to make that career choice a vocational option? Actions aimed at secondary, tertiary and professional levels are needed to raise the profile of the profession: to increase the understanding among students of what medical scientists do and to develop a career structure that ties a progression pathway to professional and vocational/academic achievements.

Science subjects are no longer popular with high school students due to perceived difficulty, no compulsion to do science to enter university and also that many courses at university no longer have science as a prerequisite to entry, instead offering bridging units as a catch up (The Australian March 1 2010). Recognising the effect of this on numbers enrolling in science, maths and engineering universities have high school visitation programmes, emerging scientist competitions and open days to display opportunities. Universities are also rushing to develop social media opportunities to communicate with the next generation of scientists to spark their interest.

While the current pathology provider operating environment is not conducive to creating more positions for scientists it is crucial that industry looks to create more career positions for scientists that have a firm structure with opportunities clearly defined for progression. Variety in activities is one way to maintain interest and while fostering careers it will be valuable if scientists are offered transferable skills that equip them for the challenges of the changing pathology landscape and promote research opportunities.

It is important for industry to make better use of talented and motivated staff so that not all of our best scientists are “promoted” to management. We are seeing more frequently, that activities previously the domain of the pathologist being undertaken by experienced scientists. With so much information generated medical scientists have already become quasi consultants in niche areas with acknowledged ability to interpret results. The authority that comes with such specialization opportunities must be fostered to retain our highest achieving scientists in the industry.

There is an opportunity for this expertise to be acknowledged in all disciplines as clinical scientist, advanced practitioner or as in the USA pathologist assistant.

Underpinning all of this is the need for competitive remuneration comparable with the earning opportunities offered to other allied health professionals. To meet these challenges it will be vital that medical scientists establish a governing body that will have a strong national presence to represent our entire profession in academic development and have a role in industrial decisions affecting its members.

The professional response

With that view in mind, a valuable initiative to address the workforce issues has been the formation of the Pathology Associations Council (PAC) that brings together representatives of professional organisations involved in pathology service delivery (Table 7).
The charter of the PAC is to represent the interests of pathology, to develop consensus documents to guide future developments, to represent the profession on national committees and to promote the profession to the public as an attractive and meaningful career. It is not a decision making body but its representation on national and federal health workforce committees provides a point of traction to bring the workforce crisis in pathology to the attention of authorities at the highest level.

Among initiatives that have been completed since its inception include the development of a Competency Based Standards (CBS) and a Scope of Practice document. These have been tabled as tier two documents with NPAAC and serve to define the contemporary role of a medical scientist and the levels of authority of technical and scientific staff for training purposes. The PAC has recognised the need to elevate the profile of the profession and has had representation at national career expos where the activities of pathologists and medical scientists are presented to school leavers and potential university entrants. It has endorsed the establishment of the Fellowship membership in the Faculty of Science of the RCPA (FFScRCPA) that recognises the contribution of elite scientists to the profession. Currently two consensus documents are in discussions that address a) the framework for the future career development and b) certification for all scientists in laboratory medicine.

**Career framework**

The career framework document is currently being circulated through the professional groups for comment and briefly, the plan encourages career progression based on learning and development i.e. it encourages attainment of professional awards and vocational training for the purpose of promotion. It will “Introduce a career framework encompassing all disciplines and employment groups within the workforce based on roles and function and linked to transferable skills and competencies.”

The scheme identiﬁes that after gaining experience in the laboratory there are senior roles for our experienced scientists to contribute as laboratory financial managers, clinical advanced practitioner scientists who are expertise their field undertaking roles traditionally performed by Pathologists and opportunities for similar progression in research and development.

**Certification for scientists**

In 2009 the PAC made representation to the National Health Professionals Registration Board on behalf of the profession to explore the possibility of registration for medical scientists. The response from the Board was that as a profession, our activities did not satisfy criteria that supported or justified registration for the foreseeable future. However it advised the PAC that medical scientists would benefit as a professional group by undertaking a programme of self regulation. With that in mind the PAC has endorsed a proposal to undertake a certification process for medical scientists. To facilitate this development a subcommittee has been formed to formulate the terms of reference and management guidelines that will be circulated to the membership for comment in the near future. The PAC agreed to proceed down this pathway as the profession needs to gather information relating to the number and demographics of scientists in the workforce. These data will provide information for future planning and provide a national hub for scientist representation.

To some extent this action will align scientists with other allied health professionals who already have accreditation or certification. It would also provide employers with improved confidence when selecting a scientist for appointment if choosing from applicants from around Australia.

This is an important initiative for the profession to adopt to assist in the formation of a representative body for the professional interests of our membership in addition to our discipline specific educational organisations.

**Conclusion**

The processes and reforms that are developing to reassure the community that the future health needs of Australians will be met are underway. Considerable funds have been allocated by the government to maintain the health workforce and increase its role in managing community wellbeing. It is a time for medical scientists to take stock as a professional body to ensure that the requirements of our ongoing contribution to healthcare are considered with the other allied health workers. Membership matters if we are going to pursue and influence policy outcomes that impact on our operation. To quote our newest PM this is a time for our own new paradigm and I would encourage you to be active in contributing to the changes which will take the profession forward beyond the aspirations of our pioneer educators such as John Saal and John Foley.
References


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Richard Hanlon
Examinations Council


The Australian. Pathology plague sparks over servicing and land grab fears. 2nd August 2010.

The Australian. Academics left off skills list despite shortage. May 26 2010.

The Australian. Students like Science but not in final years. March 1, 2010.
What’s new in haemostasis and coagulation?
Part I - The rise and fall of thrombophilia testing

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Abstract

The field of haemostasis represents an ever-developing landscape. This review is the first in a series that plans to appraise recent changes and initiatives within the area of haemostasis and related laboratory test practice. The subject of the current review is thrombophilia and its associated tests of haemostasis. In brief, haemostasis describes the mechanism whereby our bodies maintain blood flow in the circulation. Defects in haemostasis can give rise to either a tendency towards bleeding (e.g. as in haemophilia) or towards thrombosis. Both have adverse outcomes related to morbidity and mortality. Thrombophilia describes the condition whereby a predisposition towards thrombosis exists, and this can have an acquired and/or hereditary (i.e. genetic) basis. The modern specialized haemostasis laboratory has an armamentarium of tests that can be performed to assess patients defined to have ‘thrombophilia’, and consequently, mutations, polymorphisms, defects, deficiencies and/or exaggerated levels of various haemostasis related components can now be identified in many investigated patients. Nevertheless, there is limited clinical utility in this knowledge, since management generally comprises standardized care irrespective of laboratory findings. Moreover, there is a high likelihood of determining false positive findings within thrombophilia investigations that globally cautions against indiscriminant testing, and suggesting that testing patients for thrombophilia in the current clinical request landscape is actually doing patients more harm than good.

Keywords: thrombophilia, haemostasis, coagulation, laboratory tests.

Introduction

Haemostasis describes the mechanism whereby our bodies maintain blood flow in the circulation. Defects in haemostasis can give rise to either a tendency towards bleeding (e.g. as in haemophilia) or towards thrombosis (Fig 1). Both have adverse outcomes, including morbidity and in some cases mortality. Different levels of procoagulant and anticoagulant activities are present in different individuals, but providing that these are in balance, haemostasis will be at some level of homeostasis. However, if the balance tips in favor of either procoagulant or anticoagulant mechanisms, for example because of deficiencies or excesses in one or the other, then homeostasis might fail and the individual be at risk for bleeding or suffer a thrombosis depending on the direction of the imbalance (Lippi et al 2009a).

Thrombophilia describes the condition in which there is a predisposition towards thrombosis. Although thrombosis can occur both in arterial and venous circulation, the term thrombophilia tends to be used primarily for those with a tendency to thrombosis in the venous circulation, typically defined as venous thromboembolism (VTE), and most often characterized by deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Thrombophilia can have an acquired and/or hereditary (i.e. genetic) basis. Sometimes it is unclear what the basis is in any given individual, because there exists various interrelationships and because both genetic and acquired events may give rise to elevations or reductions in the same haemostasis parameters (Favaloro 2005; Mannucci 2005; Cohn et al 2007; Coppola et al 2009; Favaloro et al 2009; Previtali et al 2011).

At a basic level, thrombosis describes a failure of haemostasis to maintain homeostasis. Thrombophilia too, can therefore in many cases be identified as a failure of haemostasis. Thrombophilia can in fact be associated with a wide battery and variety of identifiable mutations, polymorphisms, defects, deficiencies and/or exaggerated levels of several haemostasis related components (Favaloro 2005; Mannucci 2005; Cohn et al 2007; Coppola et al 2009; Favaloro et al 2009; Previtali et al 2011). Accordingly, there is often a clinical desire to investigate such ‘measurable’ parameters in individual patients with a recent thrombosis and/or a ‘perceived thrombophilia’, and perhaps sometimes even in otherwise normal individuals ahead of some popularly perceived ‘at risk’ events (e.g. long haul travel).
Figure 1. Haemostasis can be seen to represent an equilibrium between procoagulant (P) forces and anticoagulant (A) forces. When these are in balance (left portion of figure), a state of homeostasis can be said to be present. To some extent, the levels of procoagulant (P) and anticoagulant (A) forces may differ between individuals (represented by triangles of different size in this figure); however, homeostasis may continue as long as these levels are in balance. When the procoagulant (P) forces exceed those of the anticoagulant (A) forces, there is a tendency to thrombosis (right portion of figure), and when the anticoagulant (A) forces exceed those of the procoagulant (P) forces, there is a tendency towards bleeding (middle portion of figure).

Overview of haemostasis and haemostasis tests

Haemostasis is commonly thought of in terms of the ‘coagulation pathways’, or as a surrogate of ‘coagulation’. In fact, haemostasis is far more complex than ‘coagulation’, and can incorporate several components unrelated to the ‘coagulation’ process, which in essence reflects clot formation. The components of haemostasis can be considered within the context of Virchow’s triad (Fig 2), or as a composite of primary haemostasis (von Willebrand factor/platelets/subendothelial components), secondary haemostasis (procoagulant ‘clotting’ factors and the natural anticoagulants) and fibrinolytic pathways (Lippi et al 2009a; Tripodi 2008; Favaloro and Lippi 2011). For the purpose of this review, the secondary haemostasis pathway will be that chiefly considered, as this is believed to be the most important in terms of thrombophilia associated with VTE risk.

Routine coagulation tests

In most haemostasis laboratories, these comprise the prothrombin time (PT)/International Normalised Ratio (INR) (reflecting the tissue factor pathway) and the activated partial thromboplastin time (APTT) (reflecting the contact pathway) (Fig 3). These basic tests are typically supplemented in some laboratories by fibrinogen assays, and occasionally thrombin time (TT) assays. Most routine test laboratories also perform D-dimer assays. These tests are sometimes performed to investigate haemostasis in patients suspected of having some potential dysfunction in the secondary haemostasis pathway, either congenital (e.g. haemophilia) or acquired (e.g. disseminated intravascular coagulation [DIC]) (Favaloro and Adcock 2008; Favaloro et al 2010; Favaloro 2010; Lippi and Favaloro 2008; Lippi et al 2008; Lippi et al 2009a; Tripodi 2008). This is because these tests are sensitive to deficiencies or defects in various pro-coagulant coagulation factors. Thus, the PT/INR is sensitive to factors (F) I, II, VII, V and X, and the APTT to factors I, II, V, VIII, IX, X, XI and XII. The single or compound deficiency or absence of most of these factors will lead to bleeding, and will occasionally define haemophilia (e.g. deficiency in FVIII gives rise to haemophilia A, whereas deficiency in FIX gives rise to haemophilia B). In contrast, an excess of some procoagulant factors (e.g. FVIII, FIX and FXI) may lead to thrombophilia. However, the PT/INR and the APTT is not very sensitive to elevations in procoagulant factors. Nevertheless, a short APTT is sometimes a sign of the elevation of some procoagulant factors, and hence also a risk factor for thrombosis (Mina et al 2010; Lippi and Favaloro 2008; Lippi et al 2010).

The PT/INR is also used to monitor vitamin K antagonists (VKAs) such as warfarin (Favaloro and Adcock 2008; Favaloro et al 2010; Lippi et al 2009b), and the APTT to monitor unfractionated heparin (Lippi and Favaloro 2008). Indeed, in normal pathology practice, these tests are more often used for monitoring anticoagulant therapy than for assessing secondary haemostasis.

Whilst the above noted tests represent the backbone of routine coagulation testing, they have limited utility within the context of specialized thrombophilia ‘investigations’, with several noted exceptions, being: (i) as noted above, the tests are used to monitor anticoagulant therapy used post thrombosis; (ii) a persistently short APTT, which as noted above may reflect the presence of highly elevated procoagulant factors such as FVIII, FIX and FXI, and hence be a marker of potential thrombophilia; (iii) the D-dimer, being a marker of recent or persistent thrombosis; (iv) where these tests are modified or adapted for use as part of specialized thrombophilia testing. The latter is briefly explored in subsequent sections.

Figure 2. Virchow's triad. Although we recognize that haemostasis, and thus the risk of bleeding or thrombosis, is constituted by the interaction of many physiological systems and pathophysiological events, the modern haemostasis laboratory is currently able to only evaluate a portion of only one point (Abnormal blood constituents) of the triangle that Virchow’s triad represents.
but a largely under-recognised ‘cause’ of diagnostic errors much less than 1% of the population. This is very important hereditary deficiencies are in fact very rare, being present in PC, PS and AT deficiencies may lead to thrombosis, such anticoagulants. However, whilst congenital (or hereditary) to measure the level and activity of these three natural formation.

example, a deficiency in PC or PS means a relative inability can lead to recurrent thrombosis, or ‘thrombophilia’. For activity. A deficiency of any of these natural anticoagulants and AT primarily expresses anti-thrombin and anti-Xa is a cofactor for PC activity (potentiating PC function), ATIII). In brief, PC acts to inactivate FV and FVIII, PS (AT; previously called antithrombin III and abbreviated ATIII). In brief, PC acts to inactivate FV and FVIII, thus causing a prolongation or extension of the procoagulant pathways, or excess thrombus formation.

Thrombophilia markers and specialised haemostasis tests used in thrombophilia investigations

As mentioned, the PT/INR and the APTT measure the in vitro activity of various procoagulant factors, and in vivo, haemostasis is a balance of procoagulant and anticoagulant mechanisms (Fig 1). A relative excess of procoagulant mechanisms (or a relative absence of anticoagulant mechanisms) will reflect a tendency towards thrombosis, whereas an excess of anticoagulant mechanisms (or a relative absence of procoagulant mechanisms) will reflect a tendency towards bleeding. To balance the procoagulant factors in vivo, haemostasis normally employs several natural anticoagulants that aim to moderate the procoagulant pathways and to prevent excessive coagulation that can lead to thrombosis. The main natural anticoagulants employed are protein C (PC), protein S (PS) and antithrombin (AT; previously called antithrombin III and abbreviated ATIII). In brief, PC acts to inactivate FV and FVIII, PS is a cofactor for PC activity (potentiating PC function), and AT primarily expresses anti-thrombin and anti-Xa activity. A deficiency of any of these natural anticoagulants can lead to recurrent thrombosis, or ‘thrombophilia’. For example, a deficiency in PC or PS means a relative inability to inactivate FV and FVIII, thus causing a prolongation or extension of the procoagulant pathways, or excess thrombus formation.

Most specialized haemostasis laboratories are able to measure the level and activity of these three natural anticoagulants. However, whilst congenital (or hereditary) PC, PS and AT deficiencies may lead to thrombosis, such hereditary deficiencies are in fact very rare, being present in much less than 1% of the population. This is very important but a largely under-recognised ‘cause’ of diagnostic errors (see later sections).

Other congenital risk factors for thrombosis include the genetic polymorphisms/mutations called prothrombin G20210A (PGA) and factor V Leiden (FVL), representing relatively ‘inactivation resistant’ procoagulant factors. Thus, the normally present AT and PC/PS anticoagulant systems are less able to inactivate these forms of FII and FV, again leading to a relative prolongation or extension of the procoagulant pathways potentially leading to thrombosis. Unlike AT, PC and PS, hereditary PGA and FVL are relatively ‘common’ in caucasians, being present in 2-7% of the white population, including Australians (Montagnana et al 2010; Pecheniuk et al 1997). Most central pathology sites have laboratories that can detect the presence of PGA and FVL, and hence these have become commonly investigated tests within the framework of thrombophilia investigations (Hertzberg 2005). The presence of FVL is also reflected in another common test used in the laboratory to assess thrombophilia, namely the activated PC (APC) resistance (APCR) assay, commonly performed using an APTT assay, or a Russell viper venom time (RVVT) or other snake venom mediated test, often modified to incorporate a FV deficient plasma mixing step to increase the assay’s sensitivity to FVL (Favaloro et al 2011a).

Acquired risk factors that we are able to measure in the haemostasis laboratory include the so-called antiphospholipid antibodies (aPL; including for example, lupus anticoagulants (LA), anticardiolipin antibodies (aCL) and anti-beta2-glycoprotein I (aB2GPI) (Favaloro and Wong 2011). The term aPL is a misnomer, since these antibodies are not directed against phospholipids per se, but rather phospholipids in association with some cofactor. The term LA is a double misnomer, since the test is neither a specific test for lupus, nor is the ‘anticoagulant’ activity detected by laboratory testing reflective of the ‘procoagulant’ effects in vivo (Favaloro and Wong 2008).

LA are measured in the laboratory most commonly using (i) the APTT assay, modified to either incorporate different reagents with low and high levels of phospholipids, or as an investigation of LA using mixing studies, and (ii) the dilute RVVT (dRVVT) assay, again modified to incorporated different reagents with low and high levels of phospholipids, and sometimes incorporating the use of mixing studies (Favaloro and Wong 2008; Favaloro and Wong 2011). There are however a wide variety of assays that may be used by laboratories, including ‘dilute’ PT assays, kaolin or silica clotting times, and platelet neutralization procedures. Within the context of this review, it is important to recognize that most of these LA assays are ‘ clot-based’ and hence sensitive to the presence of anticoagulants.

High levels of clotting factors (e.g. FVIII, FIX, FXI), dysfibrinogenemia, and hyperhomocysteinemia represent other acquired thrombophilia factors that laboratories might be able to measure. For completeness, we should however recognize that haemostasis laboratories are unable to
measure all the possible risk factors for thrombophilia. For example, acquired thrombosis risk factors that laboratories tend not to 'measure' include prolonged immobilization and hospitalization, increasing age, surgery, trauma, cancer, obesity, poor nutrition, pregnancy and postpartum, oral contraceptives, and hormone replacement therapy (Table 1) (Mannucci 2005; Lippi and Franchini 2008; Varga et al 2008; Previtali et al 2011).

Table 1. Inherited and acquired thrombophilic conditions: relative risk of venous thromboembolism (expressed by odds ratios) and prevalence in unselected cases of venous thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Inherited conditions</th>
<th>Relative risk of VTE (Odds Ratio)</th>
<th>Prevalence in unselected VTE patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>50-80x</td>
<td>unknown</td>
</tr>
<tr>
<td>Factor II Leiden</td>
<td>5-9x</td>
<td>unknown</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>6-15x</td>
<td>unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Puerperium</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
</tr>
<tr>
<td>Common malignancies</td>
</tr>
<tr>
<td>Acute/chronic illness</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Chronic smoking</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobilization or hospitalization</td>
</tr>
<tr>
<td>Trauma or fracture</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Prolonged travel</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
| **Table 2**. A summary of some pros and cons in thrombophilia testing.

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge is power</td>
<td>Knowledge is dangerous</td>
</tr>
<tr>
<td>May help explain why an individual has had a thrombosis, or why families have a tendency towards thrombosis</td>
<td>What are patients and clinicians doing with this information?</td>
</tr>
<tr>
<td>May give information on the risk of subsequent thrombosis</td>
<td>Risk of under- or over-treatment</td>
</tr>
<tr>
<td>May help identify other family members at risk</td>
<td>Insurance/genetic discrimination</td>
</tr>
<tr>
<td>Anticipatory advice (clinician can provide advice on future risk avoidance)</td>
<td>Anxiety and family issues</td>
</tr>
<tr>
<td>Occasionally influences clinical management (e.g., extended anticoagulant therapy for AT deficiency or APS)</td>
<td>Patients don't often change habits</td>
</tr>
</tbody>
</table>

Thus, on the one hand, the tests are now commonly available, and so clinicians will request them, and this may provide potentially useful information about the cause of thrombosis in some individuals, as well as identifying the potential for future thrombotic risk including that for other affected family members, particularly for hereditary defects and deficiencies (Table 2). These considerations define the reason for the progressive rise of thrombophilia testing in diagnostic practice over the past decade.

However, there also exists a long list of negatives associated with thrombophilia testing that in many cases will negate the theoretical benefits, and broadly leads to a situation where globally the disadvantages and dangers of thrombophilia testing will often outweigh the benefits (Table 2). Most clinicians, and probably most scientists, simply do not recognize the dangers of such testing.

Clinicians do not follow clinical guidelines

Despite the availability of clinical guidelines that provide recommendations on who and when to perform tests for thrombophilia (Table 3), for example the College of American Pathologists 2002, the American College of Medical Genetics (Girod et al 2001), the British Haemostasis and Thrombosis Task Force 2001 (Pengo et al 2009; Miyakis et al 2006), many clinicians simply do not follow these guidelines. Two major problems in regards to performance of these thrombophilia tests are consequently related to clinical ordering patterns, and namely poor patient selection and poor timing of test requests. The reason why these factors so greatly influence the utility of thrombophilia test outcomes is explained in the following section.

Adapted from Favaloro et al 2009.
Table 3. Recognised valid indications for thrombophilia testing.

A. General Thrombophilia testing is recommended for:
- Individuals with first VTE <50 years of age
- Recurrent VTE
- VTE at any age with a strong family history of thrombotic disease (i.e., several affected relatives or relatives with VTE <50 years of age)
- VTE in an unusual site (such as the hepatic, mesenteric, portal, and cerebral veins) at any age
- Women suffering VTE in association with pregnancy, the immediate postpartum period, or oral contraceptive use

B. General Thrombophilia testing can additionally be considered in:
- Cases of VTE in the setting of postmenopausal hormone (estrogen) therapy or unprovoked VTE for patients >50 years of age
- Thrombophilic conditions associated with obstetric complications, including fetal demise, prematurity, or fetal growth restriction

C. Appropriateness of specific LA testing can be graded according to:
- High: unprovoked VTE and (unexplained) arterial thrombosis in young patients (< 50 years of age), thrombosis at unusual sites, late pregnancy loss, any thrombosis or pregnancy morbidity in patients with autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, autoimmune thrombocytopenia, autoimmune hemolytic anaemia)
- Moderate: accidentally found prolonged APTT in asymptomatic subjects, recurrent spontaneous early pregnancy loss, provoked VTE in young patients; and
- Low: venous (VTE) or arterial thromboembolism in elderly patients.

D. APS is present if at least one of these clinical criteria and one of these laboratory criteria are present:
- Clinical criteria: (a) vascular thrombosis comprising one or more clinical objectively confirmed episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ; or (b) pregnancy morbidity comprising (i) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or (ii) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency, or (iii) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
- Laboratory criteria: (a) presence of LA on two or more occasions at least 12 weeks apart, or (b) aCL or aB2GPI of IgG and/or IgM isotype of medium or high titre present on two or more occasions at least 12 weeks apart.

Notes: Parts A and B adapted from Vergy et al 2008 and Favaloro et al 2011, as based on various guidelines including those from the College of American Pathologists (2002), the American College of Medical Genetics (Grody et al 2001), and the British Haemostasis and Thrombosis Task Force (2001). Parts C and D respectively adapted from Pengo et al 2009 and Miyakis et al 2006. Performing thrombophilia testing on patients outside of these settings substantially increases the likelihood of false-positive or false negative findings because of test limitations as well as simply by chance.

Abbreviations: aCL, anticardiolipin antibodies; aB2GPI, anti-beta2-glycoprotein antibodies; APS, antiphospholipid (antibody) syndrome; LA, lupus anticoagulant; VTE, venous thromboembolism.

Acute phase and anticoagulant effects

One major quandary is that anticoagulant therapy will affect the laboratory-detected activity of most tests related to thrombophilia investigations. This is particularly true of PC, PS and AT testing, where VKA therapy causes a reduction in the activity of PC and PS, given that they are vitamin K dependent, and heparin therapy may affect AT activity. Heparin anticoagulant therapy may also affect some clot-based PC and PS assays. Thus, VKA and heparin therapy may give rise to false identification of low PC, PS and/or AT activity, depending on the time and extent of the anticoagulation therapy, or the assays used by laboratories (Favaloro et al 2005a; Favaloro et al 2005b; Favaloro et al 2011a).

VKA and heparin therapy will also influence APCR and LA testing, and thus potentially give rise to false impression of APCR and/or LA, or in other cases may lead to false exclusion of APCR and/or LA, depending on the laboratory test patterns obtained at the time of testing. That is, for APCR and LA, both false positive and false negatives are possible, due to variable anticoagulant effects.

Another important consideration is that many of the above thrombophilia components may fall (or be ‘consumed’) during the acute phase of the thrombotic event. This is potentially true of PC and AT, for example, and thus this may give rise to a false positive (i.e. low level) finding, should testing be performed just after a thrombosis event preceding the start of anticoagulation therapy. LA may also be ‘consumed’ as part of the acute thrombotic event, giving a potential false normal (i.e. false negative) result should LA be evaluated at this time.

It is important to recognize here that the standard treatment for a thrombosis, be it a DVT or PE etc is anticoagulant therapy, typically initiated using heparin and maintained using VKAs. According, a common scenario is that a patient presenting to emergency with signs suggestive of a DVT and/or PE will be assessed accordingly and after establishing the likely presence of a thrombosis will then undergo assessment for ‘thrombophilia’ or is initiated on anti-coagulant therapy (i.e. heparin and then VKA) and then subsequently assessed for ‘thrombophilia’. Consequently, PC, PS and AT may thus present as ‘low’ values, due to consumption or an anticoagulant effect, and the patient may be labeled as having a congenital thrombophilia. Remember that the presence of true congenital deficiencies in PC, PS and AT combined in the Caucasian population is much less than 1% (Table 4). However, VKA therapy will reduce the level of PC and PS to below ‘normal levels’ in most people treated with these anticoagulants. Hence, the risk of identifying a false low PC, PS and/or AT is far more likely in test practice than identifying a true PC, PS
and/or AT deficiency (Favaloro et al 2005b; Favaloro et al 2009; Favaloro et al 2011a).

Whilst various guidelines will advise clinicians not to assess patients for these thrombophilia markers when they are on anticoagulant therapy, many clinicians do not follow these guidelines, either because they are unaware of their existence or because they do not understand the adverse consequences of these actions. Several audits of clinical practice have been undertaken and have determined that between one third and one half of all patients investigated for such thrombophilia markers are on anticoagulant therapy at the time of the investigation (Favaloro et al 2009; Favaloro et al 2011a). Even more concerning perhaps is that our laboratory has recently determined that nearly two thirds of all the ‘low’ PC and PS levels we identified in tested patients appeared to have been determined at a time that the patients were on anticoagulant therapy (Favaloro et al 2011a). Thus, in routine thrombophilia investigations, as applied globally in normal clinical practice, the risk of identifying a ‘false’ PC, PS or AT deficiency exceeds by several times (conservatively 2-5x) the rate of identification of true congenital disorders.

Table 4. Prevalence (%) of congenital risk factors for VTE in the general population and in patients with VTE.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>General population</th>
<th>Patients with VTE</th>
<th>Patients with recurrent VTE or with VTE at age &lt; 45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02 - 0.4</td>
<td>~1</td>
<td>~2-5</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.14 - 0.5</td>
<td>~3</td>
<td>1/2</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>~1</td>
<td>~2</td>
<td>1/2</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden</td>
<td>0.7</td>
<td>~2</td>
<td>10-40</td>
</tr>
<tr>
<td>Heterozygous prothrombin 302010A</td>
<td>0.7</td>
<td>1/2</td>
<td>~18</td>
</tr>
</tbody>
</table>

Adapted from Previtali et al 2011

Poor patient selection

As noted above, clinicians often order thrombophilia testing just after the thrombotic event, risking a false positive or false negative ‘consumption’ related event, or while patients are on anticoagulant therapy (e.g., heparin and/or VKA), again risking a false positive or false negative anticoagulant related event. These situations may or may not reflect proper patient selection, but they certainly reflect poor timing for the investigation.

Another issue related to identification of potentially ‘false’ congenital thrombophilia relates to the issue of poor patient selection. Clinical guidelines also specify the appropriate patient categories for investigation (Table 3), and yet ongoing evidence suggests that such guidelines are simply not being followed. Anecdotal evidence indicates, for example, testing for congenital thrombophilia markers in aged individuals. There is little benefit in evaluating for PC, PS or AT deficiencies in individuals older than 55 having had their first DVT, since should these be implicated in a thrombosis, it would be expected that such a thrombosis would have occurred before this age.

Additional evidence for ongoing and developing poor patient selection can be identified by test ordering patterns, for example as related to molecular testing. There are many adverse effects of genetic testing (Table 2) (Favaloro et al 2009; Varga et al 2008), and yet clinicians are increasingly requesting these tests, often in inappropriate patients. As noted previously, FVL is present in 2-7% (depending on the report) of all Caucasians (i.e. those suffering and those not suffering thrombotic events). However, FVL would be expected to be present in ~25% of selected familial thrombophilic cases (Tables 1 and 4). Thus, if a laboratory is identifying ~25% of the cases they have investigated as being FVL positive, then that laboratory is testing patients with familial thrombophilia (i.e. a correctly selected patient population). Alternatively, if a laboratory is identifying only 2-7% of the cases they investigated as being FVL positive, then that laboratory can be defined to be testing the normal population. It is irrational to test the normal population for FVL, since FVL is only a minor risk factor for thrombophilia, and being FVL positive will not predicate a future thrombosis, nor will identifying all individuals with FVL identify all individuals that will suffer a thrombosis. Data from our center indicates increasingly inappropriate patient selection for this test. Apparently, we were testing a true familial population in 19% but testing since that time has been increasingly headed towards that of the normal population, and currently only some 10% of cases are currently being identified as being FVL positive (Favaloro et al 2011a).

Additional evidence for poor patient selection can be identified for investigation into acquired disorders such as the antiphospholipid syndrome (APS). APS is defined by the presence of certain clinical features together with positive laboratory findings for aPL (Table 3) (Pengo et al 2009; Miyakaki et al 2006; Favaloro and Wong 2010; Favaloro and Wong 2011).

Although the presence of APS warrants investigation in appropriate patient cohorts, the investigation of patients outside these guidelines increases the risk of false positive diagnosis (Pengo et al 2009; Miyakaki et al 2006; Favaloro and Wong 2010; Favaloro and Wong 2011). This will occur when aPL are identified in otherwise asymptomatic individuals, or in individuals with insufficient clinical criteria for APS. For example, identification of LA is a common laboratory finding following investigation of a prolonged APTT, as for example identified by chance or related to ‘pre-operative’ screening of asymptomatic individuals. This should be considered a ‘false positive’ within the context of APS. A similar finding is also observed with respect to solid phase aPL testing, where transient aPL may occur in a wide range of conditions including infections.

In another recent audit from our laboratory, we determined an overall low rate (<10%) of aPL positivity among a hospital population of predominantly obstetric or...
thrombophilic patients (Favaloro et al 2011b). Interestingly, we observed no positive obstetric aPL cases, despite recognition that aPL is often found in select pregnancy morbidity conditions (Table 3). The likely explanation for this finding is again that of poor patient selection (for example, too loose an interpretation of miscarriage events by the obstetrics team to possibly include single events rather than recurrent events as a criteria for testing). This finding is likely to be replicated by other institutions and would indicate that local clinical ordering guidelines may need review.

Table 5. Causes of potential false positives and negatives when investigating thrombophilia

<table>
<thead>
<tr>
<th>False positive/ negative rate</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range effects:</td>
<td>1-6%</td>
</tr>
<tr>
<td>Anticoagulant related effects:</td>
<td>Depends on thrombophilia marker and test method used</td>
</tr>
<tr>
<td>Consumption effect:</td>
<td>1-60%</td>
</tr>
<tr>
<td>Assay variability effect:</td>
<td>Depends on thrombophilia marker and assay used</td>
</tr>
<tr>
<td>Other causes:</td>
<td>1-50%</td>
</tr>
<tr>
<td>Cumulative effects:</td>
<td>5-70%?</td>
</tr>
</tbody>
</table>

Adapted from: Favaloro et al 2005b & Favaloro et al 2009

The risks of inappropriate testing

As previously noted, there are several negative effects of thrombophilia testing (Table 2) even when the appropriate population is targeted. There are additional adverse outcomes that result from inappropriate testing, including testing of an appropriate population at the wrong time point, or testing of an inappropriate population. First, a false positive event inappropriately identifies an individual as having a disorder when they do not. Thus, a false positive PC, PS or AT deficiency, for example, whatever the cause, may result in an individual being identified as having a congenital disorder, with flow on effects for other family members and offspring. This will at the least have adverse psychological effects on patients and their families. Even identification of true events, such as FVL, may have adverse psychological effects on patients and their families at odds with the risk of the condition they have. One striking event in my mind was a phone call received from a distraught father to be, who having been told that he was FVL positive was subsequently considering the possibility of a termination for their child. In some cases, patient anticoagulant therapy may also be inappropriately applied or extended, placing said individual at increased risk of bleeding.

Similar adverse outcomes relate to identification of ‘acquired’ thrombophilia markers. Thus, symptomatic patients with APS warrant extended or lifelong anticoagulant therapy. However, ‘asymptomatic’ aPL positive patients identified by chance do not warrant anticoagulant therapy, and risk serious bleeding events should they be so treated. Therefore, an important unanswered question here is ‘are ‘asymptomatic’ aPL positive patients identified by laboratory testing being placed on inappropriate (possibly extended) anticoagulant therapy? Thus, a false identification of APS due to identification of aPL in asymptomatic or ‘non-true APS at thrombosis risk patients’ will, like congenital thrombophilia investigations, also carry adverse psychological effects, as well as subjecting such patients to the inconvenience, expense and potential bleeding risk of inappropriately applied or extended anticoagulant therapy. Alternatively, a false negative LA, for example, may deny a patient with true APS at thrombosis risk, the appropriate therapy they require to prevent a future thrombotic event. Inappropriate testing is also very wasteful of health dollars that could be better spent.

Moreover, although thrombophilia testing can identify certain defects, their identification per se may not change clinical decision-making (e.g. the extent and duration of anticoagulation therapy) or help predict recurrence. Thus, most patients with a thrombosis are treated by standardized anticoagulant therapy, and recognition of the presence of individual thrombophilia markers will often not influence this standardised treatment. In total, then, although there are valid indications for performing thrombophilia testing in select cohorts (Table 3), the net effect of widespread thrombophilia testing in poorly selected patients or timepoints would suggest that current patterns in thrombophilia testing are likely to be doing more harm than good.

Conclusion

There are several under-recognised dangers from requesting thrombophilia testing (both congenital and acquired) when clinical evidence is weak, or when patients are on anticoagulant therapy, with the main dangers being the identification of false positives and negatives (Table 5), with consequent psychological effects on both patients and other family members, and potential adverse clinical therapy issues that can lead to inconvenience, additional expense and bleeding and thrombosis risk. Finally, there are also cost/resource issues related to excessive testing and ‘over-servicing’ of patients. Ultimately, patients are best served by case-specific evaluation and management as facilitated by the most accurate clinical diagnosis, and this means targeting congenital thrombophilia test requests to those individuals and family members most likely to have thrombophilia and to benefit from testing.

The timing of test performance is also critical, with testing during anticoagulant therapy or immediately post thrombotic events to be avoided. The question of how best to educate clinicians regarding the appropriateness of test orders, including advice on the best tests to use, and when to (or when not to) order these tests, is difficult to fully address. As scientists, we can refer clinicians to published
guidelines giving advice on who and when to test (Table 3), as well as advice to not undertake thrombophilia testing in poorly selected patients with either venous thrombosis or obstetric complications. However, clinicians appear not to be heeding such advice.

In our own practice we also provide comprehensive interpretive comments on all reports related to these tests, including the potential for false identification of PC, PS and AT deficiencies, and a request that repeat testing be performed on all low test results at a time when the patient is not on any anticoagulant therapy (Table 6) (Favaloro et al 2008; Favaloro and Lippi 2010; Wong et al 2004). However, it is also possible that this advice is not being heeded. Therefore, additional avenues for continued education may be required, potentially including improved graduate training, and dissemination of guidelines and publications reflecting on ‘good versus bad’ ordering practice at interdisciplinary meetings. It is hoped that dissemination of the current report will, for example, facilitate such education.

Table 6. Sample interpretative comments for potential inclusion on test reports to help guide appropriate clinical action.

<table>
<thead>
<tr>
<th>Test:</th>
<th>Test result:</th>
<th>Sample comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithrombin</strong></td>
<td>Low level</td>
<td>Congenital deficiencies of Antithrombin are very rare. Low levels of Antithrombin may occur immediately after a thrombotic episode, during heparin therapy, in liver disease, or from a consumptive coagulopathy, haemodilution, in nephrotic syndrome, following L-asparaginase therapy or a blood collection artefact (including haemolysis). Please exclude these events and repeat one week after cessation of any anticoagulant therapy.</td>
</tr>
<tr>
<td><strong>Protein C</strong> and/or <strong>Protein S</strong></td>
<td>Low level</td>
<td>Congenital deficiencies of Protein C [and/or S] are very rare. Low levels of Protein C [and/or S] can occur immediately after a thrombotic episode, with anticoagulant or vitamin K antagonist therapy (eg warfarin), vitamin K deficiency or liver disease, on hormone replacement/oral contraceptive therapy/during pregnancy/with nephrotic syndrome - protein S or from a consumptive coagulopathy, haemodilution, or a blood collection artefact. Please exclude these events and repeat six weeks after cessation of any anticoagulant therapy.</td>
</tr>
<tr>
<td><strong>Activated Protein C Resistance</strong></td>
<td>Any result</td>
<td>Individuals with Lupus Anticoagulant, factor inhibitors, factor deficiencies, or on anticoagulant therapy (including heparin, and vitamin K antagonist therapy such as warfarin) may not provide reliable assay results.</td>
</tr>
<tr>
<td><strong>Lupus anticoagulant</strong></td>
<td>Prolongation in screen test mixing study, but negative for lupus anticoagulant by confirmation test.</td>
<td>Lupus Anticoagulant not detected. However, screening test suggested potential presence of other inhibitor type. If patient on anticoagulant therapy (vitamin K antagonist or heparin), please repeat testing when therapy ceased. Otherwise, might indicate another inhibitor (eg FV or FVIII); please discuss with laboratory as further testing may be required.</td>
</tr>
<tr>
<td><strong>Anticardiolipin antibody</strong></td>
<td>Negative IgG</td>
<td>Some patients with antiphospholipid antibody syndrome have undetectable anticardiolipin antibodies. Lupus anticoagulant testing may be indicated.</td>
</tr>
<tr>
<td></td>
<td>Positive IgG</td>
<td>The risk of clinical symptoms in the antiphospholipid antibody syndrome appears to rise with increasing levels of IgG anti-cardiolipin antibodies. Repeat testing (after 12 weeks) is recommended, as is Lupus anticoagulant testing. Transient low level/positive results generally are of questionable clinical significance.</td>
</tr>
<tr>
<td></td>
<td>Positive IgM</td>
<td>Suggest repeat testing in 12 weeks for confirmation, plus Lupus anticoagulant testing. IgM anticardiolipin antibodies are less specific than IgG anti-cardiolipin antibodies for the antiphospholipid antibody syndrome. Rheumatoid factors may produce false positive results, and transient IgM aCL may be found in a range of other inflammatory, infectious and malignant disorders.</td>
</tr>
</tbody>
</table>


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Gillian Rozenberg, FAIMS, Senior Medical Scientist, Department of Haematology, SEALS Randwick, Prince of Wales Hospital, NSW, Australia

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A difficult diagnosis of acute leukaemia in a 13-month-old infant

Gillian Rozenberg

South Eastern Sydney and Illawarra Area Health Services, Prince of Wales Hospital, Sydney, New South Wales

A 13-month-old infant with respiratory distress presented at the paediatric casualty department. On examination the infant was found to have a hepatosplenomegaly, was pale and very unwell. The infant was immediately admitted to the intensive care ward. A full blood count was performed. The results were as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>89 g/L</td>
<td>104-132 g/L</td>
</tr>
<tr>
<td>Hct</td>
<td>0.259</td>
<td>0.30-0.38</td>
</tr>
<tr>
<td>MCV</td>
<td>82.2 fL</td>
<td>70-83 fL</td>
</tr>
<tr>
<td>MCH</td>
<td>28.3 pg</td>
<td>23.1-29.4 pg</td>
</tr>
<tr>
<td>WBC</td>
<td>209.5 x 10^9/L</td>
<td>5.4-13.6 x 10^9/L</td>
</tr>
<tr>
<td>Plats</td>
<td>23 x 10^9/L</td>
<td>205-553 x 10^9/L</td>
</tr>
</tbody>
</table>

The white cell differential on this film was challenging. Approximately 45% of the cells appeared to be immature, almost blast-like however the cytoplasm was heavily granulated. Some of the neutrophils were hypogranular. The high white cell count permitted flow cytometry to be performed on the peripheral blood. The flow results revealed that the leukaemia was monocytoid. Markers CD34 and CD117 were both negative. The infant’s respiratory distress, thought to be secondary to leukaemic deposits throughout the lung, was becoming worse. Bone marrow aspiration was delayed for the time being. Thus the question arose as to whether these cells were indeed blast cells or were they more mature?

The following day a bone marrow aspiration was performed. Morphologically the marrow showed a heavy infiltrate of blast cells. The blasts clearly resembled myeloblasts. Flow cytometry was performed with the following results:

CD45+/HLA-DR+/CD4+/11b+/13+/14+/15+/33+/64+/34+/117+/MPO

The conclusion from flow cytometry was that there was predominantly a monocytic population of cells. No immature markers were identified; CD34 and CD117 were both negative as was the case in the peripheral blood. A diagnosis of acute monocytic leukaemia was made on the findings from the bone marrow.

The clinician treating the infant would now wait for the cytogenetic results to make a final diagnosis. Given the positivity of both myeloid and monocytic markers, there was still a question as to whether this was a case of myeloid or monocytic leukaemia. In the interim the consultant requested that a dual esterase, a cytochemistry stain, be performed. The dual esterase was used as a diagnostic tool prior to the use of monoclonal antibodies. It is made up of two esterases, naphthol AS-D chloroacetate esterase which is positive...
for mature and immature granulocytes and parallels the MPO reaction and α-naphthyl acetate esterase which is positive for lymphocytes and monocytes. The dual esterase clearly demonstrated that the cells in the bone marrow were monocytoid. A final diagnosis would depend on cytogenetic studies.

**Figure 3:** Bone marrow showing a positive α-naphthyl acetate esterase reaction

Cytogenetic results revealed an abnormal clone containing a translocation between the long arm of chromosome 11 and the short arm of chromosome 19.

Karyotype 46, XX, t(11;19)(q23;p13.3)

FISH analysis using the Vysis MLL breakapart probe showed a split signal indicating MLL gene rearrangement in 87% of cells. This finding confirmed the t(11;19) detected by conventional cytogenetics.

The dual esterase clearly demonstrated that the cells in the bone marrow were monocytoid. A final diagnosis would depend on cytogenetic studies.

**Reference**

CONGRATULATIONS!!
Fellowship of AIMS was awarded at the
AIMS NZIMLS SPC
on the 8th August 2011 to:

Craig Williams
Leanne Sinclair
Averil Drummond
Piero Nelva
The next two chapters discuss the composition and function of the *E. histolytica*, *G. intestinalis* and *T. vaginalis* cytoskeletons. Both chapters review cytoskeleton structure and function from the genome to the final protein products, including discussion of the structure and function of specific proteins. Major eukaryotic homologues of specific cellular cytoskeleton associated genes are also tabulated and discussed.

A chapter discussing the interpretation of analyses of the *E. histolytica* genome expression by microarray follows. Interesting comparisons in the regulation of genes are explored and compared in isolates of this species from different clinical sources and under different conditions. Comparisons of trophozoites causing liver abscess, colitis and an isolate in cyst form prove interesting, as do the comparisons of transcription in virulent and non-virulent isolates and those under environmental stress. This chapter provides an appropriate introduction to the chapter which follows, discussing the manipulation of expression in the *E. histolytica* genome. Successful down-regulation of gene expression in *E. histolytica* may open the pathway for the development of a live attenuated vaccine strain of the organism. Down-regulation of gene expression by means of anti-sense transcripts, plasmids and gene silencing by interference with messenger RNA, as well as a number of other technologies, are also reviewed.

The eighth chapter describes nuclear and chromosomal structure and replication in *G. intestinalis*. The genome is haploid and approximately 12 Mb in size (compare to the massive *T. vaginalis* genome). The protozoan has two nuclei, both of which replicate at the same time, and both of which are transcriptionally active. Particularly interesting are the biological arguments for and against the possibility that Giardia may in fact reproduce (at least in some cases) sexually.

The final chapter is, somewhat oddly, the only one dedicated to *Blastocystis hominis*. The mitochondrion like organelles, including the organelar genome and metabolic modeling, are discussed. Brief attention is devoted to the multiple genospecies of *B. hominis*, and the possible role that potential differences in pathogenicity between these genospecies may have in explaining controversy over the role of this organism in human disease. Metabolic modeling and future directions are competently reviewed as well.

This book represents a useful resource for those conducting research specifically in the area of genomics, metabolomics and gene expression in any of the discussed anaerobic protozoa. It is well written, well referenced and very up to date in its content. I found the habit of most
authors to refer to the organisms examined by genus only (Giardia instead of G. intestinalis, Blastocystis instead of B. hominis, etc), or by taxonomically incorrect or superseded terms (G. lamblia) somewhat frustrating in a specifically academic text aimed at experts and those training to be experts in the field. However, this is a minor criticism. It is a great shame that the text did not include at least one chapter devoted to Dientamoeba fragilis, now recognized as a common human pathogen, and an important organism requiring further research. Apart from this unfortunate omission, the text has achieved its goal of providing a single comprehensive review of current research in the field of anaerobic genomics and molecular biology admirably.

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Pathology of the Lungs
Elsevier
B Corrin and AG Nicholson
Hard cover VI + 778 pages
ISBN: 978-0-7020-3369-8
AUD$299.00

The third edition of Pathology of the Lungs is another outstanding publication by Elsevier with the intent to provide a practical guide to assist the general surgical pathologist and the pulmonary pathologist in the diagnosis and interpretation of lung and pleural specimens encountered on a routine basis. The presentation format is also aimed at thoracic clinicians, radiologists and surgeons as well as general histopathologists.

The main text has been authored by two subject matter experts (Chapters 1-10, pp. 1-506; Chapters 12-13, pp. 531-752): Bryan Corrin, FRCPath, Emeritus Professor of Pathology, London University; Honorary Senior Clinical Research Fellow, National Heart and Lung Institute, Imperial College London; Honorary Consultant Pathologist, Royal Brompton Hospital; and Andrew G Nicholson, FRCPath, Consultant Histopathologist, Royal Brompton and Harefield NHS Foundation Trust (RBHNFT); Professor of Respiratory Pathology, National Heart and Lung Institute, Imperial College London. One chapter has been revised by two expert contributors (Chapter 11, pp. 509-529): Margaret Burke, FRCPath, Honorary Consultant Histopathologist, RBHNFT; and Alexandra Rice, FRCPath, Consultant Histopathologist, RBHNFT; Honorary Senior Lecturer, Imperial College London. The text is divided into 13 chapters (Chapters 1-13, pp. 1-752) and is supported by 745 figures—these include gross anatomy photographs, photomicrographs, transmission electron micrographs, scanning electron micrographs, medical illustrations by Frank Henry Netter, high-resolution computed tomography images and radiographs, 104 colour tables and 50 commentary boxes in order to aid the readers to realise complex concepts and highlight significant points. Most of light microscopic analyses were based on haematoxylin-eosin stained tissue sections to aid interpretation, however, special stains and immunocytochemistry were used to further demonstrate key diagnostic features. A total of 7973 reference titles are presented in the text. It has one table of contents (p. vi), one subject index (pp. 765-778) and one appendix (pp. 753-763). One of the competitive advantages of Elsevier’s medical publication is the ability to access the entire book online. As an Expert Consult title (www.expertconsult.com), the reader has fully searchable contents capability until the release of next edition or until the current edition is no longer available by Elsevier.

The first two chapters provide the introductory information that readers should read prior to moving to the chapters on disease processes of the lung. Chapter 1 (pp. 1-37) covers the structure of the normal lungs. This introductory chapter is brilliantly written and supported by medical illustrations by a world renowned medical illustrator, Frank Henry Netter, MD, well-known for his publication Netter’s Atlas of Human Anatomy. There are many perfectly taken transmission electron micrographs and scanning electron micrographs are used to reinforce points. This chapter is particularly useful for medical scientists who wish to revise their knowledge on the basic structure of the lungs. Chapter 2 (pp. 39-90) provides an excellent coverage on the development of the lungs; perinatal and developmental lung disease. This chapter in fact is particularly useful for medical scientists who wish to further understand the embryological basis of developmental lung diseases. Chapter 3 (pp. 91-134) contains diseases of the conductive airways. This short chapter is well-written and contains 438 references for further readings. Chapter 4 (pp. 135-153) concentrates on acute alveolar injury caused by a wide range of pulmonary insults. Chapter 5 (pp. 155-262) is on infectious diseases. This chapter is divided further into five sections and has key information on viral, bacterial, fungal and parasitic infections. These sections are particularly useful for medical scientists in Microbiology. Each disorder is further presented into three headings: clinical features, pathogenesis, and histopathology. The section on viral, mycoplasmal and rickettsial infections covers viral infections caused by orthomyxovirus (influenza virus), paramyxoviruses (parainfluenza virus, measles virus and respiratory syncytial virus), adenoviruses, herpeviruses (cytomegalovirus, varicella-zoster virus and herpes simplex virus) and formerly variola virus (smallpox); and rickettsial infection caused by coccobacillary organisms genera include Rickettsia, Barorella (formerly Rochalimaea) and Coxiella. The subsequent sections
detail acute and chronic bacterial infections of the lungs. These include fungal infections from pathogenic fungi such as Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis and Paracoccidioides brasiliensis; and parasitic infections by certain protozoa, helminths and arthropods.

Chapters 6 to 13 (pp. 263-752) are particularly useful for medical scientists in Histopathology who handle tissues of the lung routinely. Chapter 6 (pp. 263-326) is 'diffuse parenchymal disease of the lung'. Chapter 7 (pp. 327-399) is 'occupational, environmental and iatrogenic lung disease'. Chapter 8 (pp. 401-457) is 'vascular disease'. Chapter 9 (pp. 459-470) is 'pulmonary eosinophilia'. Chapter 10 (pp. 471-507) is 'pulmonary manifestations of systemic disease'. Chapter 11 (pp. 509-529) is 'lung transplantation'. Chapter 12 (pp. 531-705) is 'tumours'. This chapter is further divided into seven sections describing carcinoma of the lung; other epithelial tumours; soft-tissue tumours; lymphoproliferative disease; miscellaneous tumours; secondary tumours of the lungs; and tumour-like conditions. This chapter is well-written and supported by 2060 references. One of most significant updates in this chapter is the revised World Health Organization histological classification of pulmonary adenocarcinoma proposed by the International Association for the Study of Lung Cancer in conjunction with the American Thoracic Society and European Respiratory Society. Chapter 13 (pp. 707-752) is 'pleura and chest wall'. Chapters 12 and 13 should be read in conjunction with Tumours and Tumours-Like Conditions of the Lung and Pleura by César A Moran, MD, and Saul Suster, MD, Elsevier. The appendix (pp. 753-763) contains a section on the processing of lung specimens. It is apparent that lung specimens are obtained by a variety of procedures and vary greatly in size, therefore special recommendations and considerations are described. The section on special light microscopic procedures describes the relevant special stains and immunocytochemical markers used in pulmonary pathology. Another useful section is on bronchoalveolar lavage cell counts in various lung diseases. This section provides practical guidance to medical scientists who handle small volume lavage samples that are associated with infectious, neoplastic and interstitial lung diseases.

Although the technical presentation of this book is almost perfect, several areas could be improved in the next edition. Firstly, each figure commentary should use a justified format for the text. This enables the text to align perfectly to the figures. Secondly, each photomicrograph commentary should contain the magnification factor for accurate interpretation. Thirdly, a list of abbreviations used in this text should be provided to aid the readers in clarifying commonly used terms. Fourthly, there is a total of 7973 references presented in this book, so it would be great if the next edition will reduce the font size of the reference titles to reduce the total page numbers. Lastly, the authors should use more medical illustrations by Frank Henry Netter, MD, throughout the text to clarify structural concepts. Furthermore, there are several relevant medical illustrations from The A to Z of the Heart by Amanda I. Neill, PhD, should be included to support the text.

This book has achieved a grade of ‘high distinction’ in our opinion. It displays consistent standards of excellence throughout. Firstly, each chapter has a chapter contents page at the beginning to aid the readers to search for information. Secondly, there is a wide amount of relevant information gathered through the literature; a total of 7973 references are available for further readings. Thirdly, it certainly identifies the most relevant issues and problems related to addressing the intent of this book. This is done in an insightful way indicating a thorough understanding of the topics. Fourthly, there is a clear and logical flow of information throughout the various chapters of the main text. Fifthly, the book is professionally presented with correctly presented referencing and good use of suitable academic language throughout. Lastly, it shows a consistent originality and excellence in analysis, evaluation and summaries that sets it apart from others who competently to cover the topic.

This book has certainly achieved its aim to provide a practical guidance to assist the readers in the diagnosis and interpretation of lung and pleural specimens encountered on a regular basis. In sum, it is highly suitable for health professionals who routinely handle lung specimens, so it is relevant to medical scientists in Microbiology, Cytopathology and Histopathology. Overall, it is a perfect resource for routine reference for medical scientists who handle lung and pleura specimens at bench level and for medical scientists who wish to keep up-to-date on the latest development in pathology of the lungs.

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Tumors and Tumor-Like Conditions of the Lung and Pleura
Elsevier
CA Moran and S Suster
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ISBN: 978-1-4160-3624-1
AUD$244.00

The first edition of Tumors and Tumor-Like Conditions of the Lung and Pleura is an outstanding publication written by practitioners for practitioners. This publication was developed with the intent to provide a practical visual guide to the accurate diagnosis of the tumours and tumour-like conditions that affect the lung and pleura. This superb visual resource enhances the thoracic diagnosis capabilities to the working bench level.

The main text has been authored by two subject matter experts (Chapters 3-13, pp. 50-436; and Chapter 15, pp. 447-453); César A Moran, MD, Professor of Pathology and Thoracic Head and Neck Medical Oncology, Deputy Chair of Pathology, Department of Pathology, The University of Texas, MD Anderson Cancer Center, Houston, Texas, United States; and Saul Suster, MD, Professor and Chair, Department of Pathology and Laboratory Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, United States. The content is further contributed by three more leading experts from the MD Anderson Cancer Center: Edith M Marom, MD, Professor of Diagnostic Radiology, Department of Diagnostic Imaging (Chapter 1, pp. 1-40); David J Stewart, MD, Professor and Deputy Chair, Department of Thoracic and Head and Neck Oncology (Chapter 14, pp. 437-453); and Garret L. Walsh, MD, Professor of Surgery, Department of Thoracic Surgery (Chapter 2, pp. 41-49). This book is logically presented into 15 chapters. The text is supported by a sufficient number of tables (16 tables) and figures (>900 figures) to highlight significant points and to aid in clarification of complex concepts. Almost all figures are in colour, these include gross anatomy photographs, photomicrographs, radiographs and contrast-enhanced computed tomography (CT) images. Most light microscopic analyses were based on haematoxylin-eosin stained tissue sections to aid interpretation. It has one contents page (p. xi) and one subject index (pp. 455-465). As an Expert Consult title (www.expertconsult.com), this edition comes with access to the full text online with fully searchable contents capability. This is however only available until the release of next edition or until the current edition is no longer available by Elsevier.

The text is divided into 15 chapters and based on the different families of tumours. The text focuses on the morphologic approach while reinforced with rich radiologic, surgical and oncologic information. Each chapter is collaboratively written resulting in a uniform presentation with minimised repetition. The chapters are generally presented in five main headings. Starting from historical background with the intent of providing classification and definition clarification; clinical features with the intent of providing clinical signs and symptoms; gross features with the intent of providing a macroscopic understanding; and immunohistochemical features with the intent of providing key identification features. Advanced techniques were included in several immunohistochemical features sections. Chapter 1 (pp. 1-40) concentrates on the lung and pleural tumour imaging. Techniques include CT, magnetic resonance imaging, ultrasonography, positron emission tomography (PET) and CT-PET. This chapter allows the selection of the ideal imaging modality for each case. Chapter 2 (pp. 41-49) describes how surgeons approach the patient with a thoracic malignancy and the use of staging interventions. Chapters 3 to 11 (pp. 51-348) contain: non-small cell carcinomas; salivary gland-type tumours; neuroendocrine tumours of the lung, biphasic tumours; mesenchyme tumours; vascular tumour; tumours derived from presumed ectopic tissues; lymphoproliferative tumours; and tumours of uncertain histogenesis. These chapters provide an excellent understanding of tumours of the lung. Chapter 12 (pp. 349-387) contains benign tumours and tumour-like lesions of the lung. Chapter 13 (pp. 387-436) contains information primarily on primary lesions of the pleura. Chapter 14 (pp. 437-446) contains clinical management of lung cancer and the differences in management between non-small cell lung cancer and small cell lung cancer. Chapter 15 (pp. 447-453) contains handling and grossing of larger cases. Three cases are described: extrapleural pneumonectomy; resections with staple line; and bronchial obstructing tumours in this short chapter. This chapter provides valuable information for medical scientists who are involved in preparing gross specimens for histologic assessment. Practical considerations and recommended techniques are described with illustrations.

There are few areas that could be improved in the next edition of this text. The table of contents should list up to two levels of internal headings and should include a list of abbreviations used in this text to aid the readers in clarifying commonly used terms. It would be helpful to readers if each photomicrograph commentary contained the magnification factor for accurate interpretation. A perfect example of photomicrograph commentary format can be sought from the third edition of Microscopic Haematology: a Practical Guide for the Laboratory by Gillian Rozenberg, FAIMS. Lastly, the references could have been presented in smaller font size to reduce the number of pages.

The target audiences of this publication are surgical pathologists, oncologists, surgeons, radiographers and
radiologists, enabling them to formulate an accurate diagnosis; fortunately it is highly relevant to medical scientists who handle lung and pleura specimens at bench level and for medical scientists who are keen to keep themselves current of the latest diagnoses and techniques involved. The cost for this text is justifiable for such well-complied information. It is highly recommended to health professionals who are associated with diagnosis of the lung and pleura tumours and tumour-like conditions. In sum, this publication is well written and has certainly achieved the intent of the authors.

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**Frontiers of Hormone Research**

**Volume 35**

**Pituitary Today Molecular, Physiological and Clinical Aspects**

E Arzt, M Bronstein, M Guitelman

Karger

Hard cover  184 pages

ISBN: 978-3-8055-8353-4

RRP: US $156.00

This book was published soon after the ‘Pituitary Today’ meeting held in Argentina in late 2005. Many of the presentations of that meeting have been incorporated into the book, injecting latest findings not yet published in other text books.

It is fitting that the opening chapter is entitled **Implications of Pituitary Tropic Status on Tumour Development** because the commonest pathology of the pituitary that we see is tumours. The chapter discusses candidate genes involved in tumorigenesis and tropic status as a modulator of tumours, with a brief discussion on transgenic mice, giving a rare insight into the molecular aspects of pituitary tumours.

It is fascinating to read about anterior pituitary cell renewal in response to changing oestradiol levels during the oestrus cycle, leading to the chapter on the genesis of prolactinomas, in animals treated with oestrogen. The next chapter expands on the mouse model with dopaminergic D2 receptor knockout mouse. Furthermore, these chapters discuss various tumour growth factors including vascular endothelial growth factor as well as anti angiogenic molecules derived from prolactin, that may play a significant role in the growth of pituitary tumours.

There are discussions on the molecular mechanisms of pituitary tissue growth and differentiation, novel regulatory factors such as ghrelin and regulation of the hypothalamic pituitary adrenal axis and growth hormone by oestrogen. More clinically oriented chapters discuss the important issue of how long to follow up prolactinoma patients for, treatment outcome for acromegaly, ectopic ACTH syndrome and diagnosis and treatment of Cushing disease.

I found all chapters fascinating to read. This book is aimed at a wide audience, including basic researchers, biochemists, endocrinologists and neurosurgeons who are interested in the molecular basis to pituitary disease. While the book meets its target of compiling a series of fascinating lectures on cutting edge research in the area, the organisation of chapters could have been improved. I found the alternating basic research and more clinically oriented chapters distracting, and harder to read. I would have preferred the basic science chapters to be in the beginning of the book and all the clinically oriented chapters to be together. The chapters did not follow on logically from each other. However, if the book has been intended as a reference then the order of chapters may not be an issue.

I especially enjoyed reading the clinically oriented chapters, particularly the chapters on Ectopic ACTH syndromes and The Diagnosis and Treatment of Cushing Disease. The chapter on gene therapy for neuroendocrine system opens a window into the future. I believe that this book will be useful to any endocrine library, as well as to an endocrine laboratory collection of reference books.

Dr Devika Thomas
Chemical Pathology Senior Registrar
SA Pathology, Frome Road, SA 5000
Following is a list of books available for review by resource consultants and members of the Institute with particular expertise in the field.

The reviewer is invited to retain the complimentary copy of the book once the review is received.

As per our agreement with the book publishing companies, complimentary books are submitted to the Institute provided that all reviews are published in the Australian Journal of Medical Science. These reviews must be of a high quality as buying decisions and the reputation of the book and author are important considerations.

Books not requested will be allocated at discretion of the Editors for the Australian Journal of Medical Science. Reviews should be 300 to 700 words depending on the volume of the book. Time limit for return of review is six weeks.

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Latest Additions:
- Molecular Virology and Control of Flaviviruses
- Endocrine Development Volume 21: Cartilage and Bone Development and Its Disorders
- Non-coding of RNAs and Epigenetic Regulation of Gene Expression Drivers of Natural Selection
- Palliative Care for Infants, Children and Adolescents


7. Contributions to Microbiology Volume 17: Sepsis - Pro-Inflammatory and Anti-Inflammatory Responses - Good, Bad or Ugly? Edited by H. Herweal and A.Egesten. Karger. Xi+162 pages


42. The Regulatory Genome: Gene Regulatory Networks in Development and Evolution author EH Davidson. Elsevier Australia. 289 pages.


Australian Professional Acknowledgement of Continuing Education (APACE)

5 APACE Group 1 credits per set of questions will be awarded if at least 8 out of 10 questions are answered correctly. 40 credits maximum per year can be claimed.

Journal-based CPD No. 30
Page 1 of 2

Questions relating to "A healthier future for all Australian" Intregrating laboratory medicine into the vision, page 122 of this issue.

1. Australians enjoy the highest life expectancy in the world. True/False

2. Chronic health issues in Australians are collectively responsible for 70% of health expenditure. True/False

3. Pathology testing by GPs is the mainstay of preventative health and the early detection of disease in the Australian Health system. True/False

4. The pathology test is an over-valued commodity. True/False

5. The enrolment of trainees required to sustain the medical scientists workforce would have to increase by 50% and be maintained at that number each year to satisfy future demand. True/False

6. The operational environment of the laboratory results in pressure to increase productivity and prevents innovation. True/False

7. PoCT creates an opportunity for the laboratory to extend its traditional service to training, competence checking, quality control and maintenance to ensure patient safety is assured. True/False

8. Activities previously the domain of the pathologist are increasingly being undertaken by experienced scientists and medical scientists have become quasi consultants in niche areas. True/False

9. The Pathology Associations Council has recognised the need to elevate the profile of the profession of medical science. True/False

10. The National Health Professionals Registration Board determined that the medical scientist profession satisfied criteria that justified registration in the foreseeable future. True/False

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Journal-based CPD No.30  
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Questions relating to What's new in haemostasis and coagulation? Part I - The rise and fall of thrombophilia testing, page 131 of this issue.

1. The PT/INR is sensitive to factors (F) I, II, VII, V and X and the APTT to factors (F) I, II, V, VIII, IX, X, XI and XII.  
   True/False

2. The PT/INR and the APTT are very sensitive to elevations in procoagulant factors.  
   True/False

3. PT/INR and APTT are more often used for monitoring anticoagulant therapy than assessing secondary haemostasis.  
   True/False

4. A deficiency in protein C (PC) or protein S (PS) means a relative inability to activate FV and FVIII.  
   True/False

5. Clinicians always follow the clinical guidelines that provide recommendations on when and on whom to perform tests for thrombophilia.  
   True/False

6. For activated protein C resistance (APCR) and lupus anticoagulant (LA) both false positive and false negative results are possible.  
   True/False

7. Audits of clinical practice have determined that between one third and one half of all patients investigated for thrombophilia markers are on anticoagulant therapy at the time of the investigation.  
   True/False

8. There is much benefit in evaluating for PC, PS or AT (antithrombin) deficiencies in individuals older than 55 having their first DVT.  
   True/False

9. Most patients with a thrombosis are treated by standardized anticoagulant therapy however the recognition of individual thrombophilia markers will usually influence this standardized treatment.  
   True/False

10. Timing of test performance is critical, testing during anticoagulant therapy or just post thrombotic events should be avoided.  
    True/False

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YEAR 2011

DECEMBER 10 – 13
American Society of Hematology Meeting
SAN DIEGO  USA

YEAR 2012

JANUARY 31 – FEBRUARY 1
FiLMS
BIRMINGHAM  UNITED KINGDOM

APRIL 27 – 29
South West AIMS Annual Conference
WAGGA WAGGA  NSW  AUSTRALIA

JUNE 8 – 10
AIMS Tropical Division Cairns Scientific Conference
Venue to be confirmed
CAIRNS  QLD  AUSTRALIA

JULY 22 – 25
Human Genetics Society of Australasia
36th Annual Scientific Meeting
National Convention Centre
CANBERRA  ACT  AUSTRALIA
www.hgsa.org.au  Email: hgsa@wsm.com.au

SEPTEMBER 24 – 27
NSM 2012 AIMS/NSM Meeting
Darwin Convention Centre
DARWIN  NT  AUSTRALIA

OCTOBER 28 – 31
HAA Meeting
MELBOURNE  VIC  AUSTRALIA

NOVEMBER 15 – 18
AACB Annual Scientific Meeting
MELBOURNE  VIC  AUSTRALIA

NOVEMBER 15 – 18
IFCC General Conference
KUALA LUMPUR  MALAYSIA

DECEMBER 8 – 11
American Society of Hematology Annual Meeting
ATLANTA  GEORGIA  USA

YEAR 2013

NOVEMBER 17 – 20
APFCB Congress
BALI  INDONESIA

OCTOBER 20 – 23
HAA Meeting
GOLD COAST  QLD  AUSTRALIA
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<td>M. Shephard</td>
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It appears that the genetic programming of humans and other complex organisms has been misunderstood for the past 50 years, because of the assumption that most genetic information is transacted by proteins, leading to the derived assumption that most intronic, intergenic and retrotransposed sequences in eukaryotic genomes are non-functional. Humans are comprised of ~100 trillion cells organised into a myriad of different muscles, bones and organs, each with a precise architecture. Surprisingly, however, the human genome appears to contain only about 20,000 protein-coding genes, similar in number and with largely orthologous functions as those in simple nematodes that have only 1,000 cells. On the other hand, the extent of non-protein-coding DNA increases with increasing complexity, reaching 98.8% in humans, presumably to contain an expanded regulatory system that underpins more complex development. Recent whole genome analyses have shown that the vast majority of these sequences are dynamically transcribed, mainly into long and short non-protein-coding RNAs, of which there are tens if not hundreds of thousands that show specific expression patterns and subcellular locations. These include not only miRNAs, but also new classes of small RNAs derived from transcription initiation sites and splice sites, and new classes of long ncRNAs derived from developmental enhancers and post-transcriptional processing of mRNAs. The emerging evidence indicates that these RNAs form a massive hidden network of regulatory information to control gene expression at various levels, including the site-specificity of the chromatin-modifying complexes that underpin developmental trajectories and cognitive function, and that these regulatory RNAs are dysregulated in cancer and other complex diseases. While it is relatively easy to revert cells back to a pluripotent state, the amount of information required to control the forward processes of 4-dimensional differentiation and development is enormous. It is also becoming evident that animals, particularly primates, have superimposed plasticity on these RNA regulatory systems by RNA editing, and that this is the molecular basis of the environment-epigenome interactions that underpin brain function and (in all likelihood) complex diseases. Ret- rotransposons also appear to contribute to genomic plasticity and somatic mosaicism, especially in the brain. Moreover, there is increasing evidence that regulatory RNAs are trafficked between cells and even generations. Thus, it appears that most assumptions about the nature and structure of regulatory information in complex organisms have been incorrect, and that what was dismissed as ‘junk’ because it was not understood will hold the key to understanding human evolution, embryonic development, phenotypic diversity and cognition, with far-reaching implications for science, medicine and biotechnology.

Medical Science in Australia is a relatively low-profile and undervalued profession. An analysis of the industry will attempt to examine the quality of this service and to also strive to improve the system we work in. The study will be the backdrop for several case presentations where pathology testing may either aid or distract diagnosis and management.

Methods: A background of who drowned, when, where and why will be given. Simple known prevention strategies will be briefly discussed. This will be the backdrop for several case presentations where pathology testing can either aid or distract diagnosis and management.

Conclusions: Results of pathology testing in drowning and near drowning require careful interpretation. They require an understanding of the event, the pathophysiology and the demographics.

Advantages of the study: The study aims to assess the intervention to improve integrity of specimen identification. Consideration was also to be given if this was cost effective.

Methods: A pseudo-randomised, prospective interventional study was conducted in our tertiary ED, incorporating a before and after design. Data were collected by direct observation of staff during the process of patient identification for the collection and labelling of pathology specimens. The intervention consisted of an education program and the introduction of a new technology. Data were collected before and following the intervention with two arms looking at education alone versus education and new technology. Errors in the identification process and actual pathology labelling errors were compared between the pre- and post-intervention stages. Health economist review of process changes, results and costs would guide if cost effective.

Results: The study showed all components of the identification and labelling system were significantly improved following the intervention. In particular, application of armbands prior to sample collection was markedly increased from 35.7% to 89.7% following the combined intervention of education and scanning device. Asking the patient to state their name increased from 25% to 92.8% and asking the patient to state their date of birth rose from 21.9% to 92.8%. A less dramatic increase was seen in bedside labelling and the generation of forms prior to taking the pathology sample.

Conclusion: A substantial error rate was observed in all steps of the patient identification and sample labelling processes. Education alone improved performance and decreased error rates in steps of patient identification and was further augmented by the introduction of bedside armband scanning and labelling devices. The study suggests cost benefit may not be met for the technology intervention. This requires further study and consideration of community expectations for patient safety.
Case study 1: I describe microsporidian infections in the eye and in a renal transplant. TEM showed spores with a double nucleus and polar tube coils arranged in two single rows, each with 5-7 tubule profiles. The organism was identified as Vittaforma corneae.

Case study 2: A renal patient who had recently had episodes of diarrhoea presented two months post-transplant with granulomas in her transplanted kidney. Light microscopy of renal tissue showed numerous foci of interstitial inflammation containing gram-positive micro-organisms. TEM identified microsporidial spores with two single rows of 4-5 polar tubes. The organisms were provisionally identified as Encephalitozoon intestinalis which is common in enteric infections. The patient was also infected with BK virus.

A trawl through the bacterial, viral and parasitic causes of waterborne infections secondary to aspiration, ingestion or contact with water with special reference to the dangers of flooding, the infections that increase after flooding and local infections and outbreaks pertinent to Queensland.

S9: WATER BORNE INFECTIONS
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S10: MOSQUITO-BORNE PATHOGENS AND THE THREAT TO AUSTRALIA
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S11: SPECIATION OF ARSENIC IN FOODS
H. Olszowy
Henry_Olszowy@health.qld.gov.au

Toxic elements such as arsenic, chromium, mercury etc can be found in foods, water, soils and the air we breathe and can pose a health risk to humans, animals and the environment. Traditionally, health risk assessments associated with toxic elements involved the determination of "total element concentrations" and risk to human health was assessed by comparison of results with guideline values. This simplistic approach has been challenged on the basis that some species of a particular element are significantly more toxic than other species of the same element. For example, inorganic AsIII is 300 times more toxic than arsenobetaine which is a commonly occurring organic form of arsenic found in seafood such as fish, crustacean, mussels etc. In this respect, a meaningful health risk assessment can only be made if data on species profiles, rather than "total" element concentrations, is made available.

The Inorganics laboratory at QHFSS has successfully speciated arsenic in urine and water samples. Separation of the species was achieved by high performance liquid chromatography (HPLC) and individual species were subsequently detected by inductively coupled plasma mass spectrometry (ICPMS) by monitoring the 75As intensity. Quantitative extraction of all arsenic species from solid materials such as fish tissue has also been achieved and involves degradation of tissue using an enzyme attack technique. The species of interest include inorganic AsIII and AsV as well as organic species monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), arsenocholine and arsenobetaine. This paper describes aspects of arsenic in the environment and the methodology employed for speciation of arsenic.
S12: INTRODUCTION TO AUTOMATION AND IMAGING IN LIQUID BASED CYTOLOGY

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The RCPA Cytopathology QAP provides testing material to more than 200 laboratories within Australia and overseas, and encompasses both gynaecological and non gynaecological cytology. Laboratories may enrol in any or all of five modules: conventional gynaecological, liquid based gynaecological, general non-gynaecological and fine needle aspiration.

Until now testing material has comprised glass slides which are sourced from participating laboratories. In recent years, the program has encountered some difficulty in obtaining sufficient high quality cases to ensure efficient distribution of both gynaecological and non gynaecological slide surveys.

Following a pilot program in 2009 and 2010, in 2011, virtual cases were into the non gynaecological modules for the first time. The use of virtual microscopy in proficiency testing is not new but presents some specific challenges to cytology proficiency testing. The combination of a high degree of depth of focus and the presence of hyperchromatic crowded epithelial cells in cytology preparations can make digitizing the entire material difficult. This means that creating a virtual proficiency test for Cytopathology that closely mirrors the actual work environment is challenging.

Preliminary results from virtual surveys will be presented as well as alternative strategies currently being considered for the use of virtual microscopy in the Cytopathology QAP.

S13: GLOBAL WARMING IMPACT ON DISEASES

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Climate change and global warming are very much in the forefront of the minds of the Australian public at present with the on-going debate about the introduction of a carbon tax. Most people think of rising sea levels, melting of the polar ice-caps and increased temperatures when asked about climate change. However, all of these things have a big impact on the environment (witness the increased number of extreme weather events in the past few years) and these in turn affect a whole range of things upon which humans rely, such as the food supply (loss of habitat for growing traditional crops, resulting in widespread famine) and the movement of large numbers of people in search of food, and the emergence of new areas suitable for cultivation), the movement of viral and bacterial vectors into new geographical areas, and the increased incidence of common pathogens such as Salmonella and Escherichia coli, as temperatures continue to rise and the summer period grows longer alongside warmer winters. This presentation will examine some of these issues and look at specific examples where there might be evidence of a trend in changes of incidence which could be linked to global warming.

S14: TWO WATERBORNE OUTBREAKS OF SALMONELLOSIS IN DRINKING WATER IN RURAL QUEENSLAND

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Reports of waterborne outbreaks of gastroenteritis associated with drinking water are rare in Australia primarily because of the quality of water supplies and the recognised importance of high standard drinking water guidelines by Australian Authorities. Surveillance conducted by OzFoodNet between 2001 and 2007 identified only ten drinking water outbreaks in Australia, most of which were linked to tankwater or bore water supplies. One was a community-wide outbreak of salmonellosis caused by contamination of a reticulated borewater system in a rural town in Queensland (Popn ~ 6500). Twenty cases of Salmonella Saintpaul infection were reported among residents or visitors to this town over a four week period in October 2005. Approximately one third of 91 surveyed households in the town had at least one household member with an acute gastrointestinal illness during the outbreak period. The suspected source of the outbreak was effluent runoff from a nearby abattoir that seeped into one of the ten bores that were supplying water to the town water system at that time. A case-control study found a significant association between illness and consumption of unboiled tap water. Salmonella Chester and E. coli were detected in the drinking water whilst Salmonella Saintpaul and S. Chester were detected in effluent from the abattoir.

The same rural town experienced a second outbreak of salmonellosis earlier this year. Twenty-six cases of a rare MLVA strain of Salmonella Typhimurium (STm) infection were reported by the Queensland Health Public Health Microbiology Laboratory between 4 March and 26 April. The same strain of STm and Salmonella Subsp.1 were detected in drinking water samples collected during the investigation. The source of this outbreak was unable to be confirmed. Investigation methods, epidemiological and microbiological findings and public health control and prevention measures for both outbreaks will be presented.

S15: CASE STUDIES

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Introduction: Numerous biochemical cases will be examined with the underlying biochemical possibilities explored and explained. Particular aspects of water trauma cases will be examined, including the presentation of an unconscious young male at a local ICU, and the investigations that were performed to help clarify the circumstances surrounding this man’s accident.

Conclusions: Biochemical results are rarely diagnostic in their own right. As with most pathology disciplines, optimal interpretation requires a detailed clinical history, useful clinical notes, ordering of suitable tests, and a sound knowledge of biochemical principles.

S16: HISTORY OF PATHOLOGY

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The history of pathology can be traced to early applications of the scientific method to the field of medicine: systematic human dissection, organ pathology, cellular pathology, bacteriology, bodily fluid and intracellular biochemistry, and molecular pathology. Like medicine, however, its development has occurred in fits and starts, and is often a retrospective compendium linking the biographies of significant individual contributors. Within this history, it is only relatively recently that diagnostic pathology separated from experimental pathology, set up its own societies and journals, and received recognition (and pay) for its professional staff.

In the 1960s through to the 1980s, advances in automation, information management and quality improvement permitted rapid expansion in the provision of diagnostic services. Moreover, the increasing technical complexity and the professional subdivision of scientific pathology distanced diagnostic pathology from clinical medicine. The constraints and reallocation of government funding for pathology services, combined with environmental conditions that favoured organisational transformation rather than incrementalism, led to private laboratory takeovers, mergers and closures, and for public laboratories, external benchmarking, competitive tendering and privatisation or state corporatisation of diagnostic pathology services. Corporatisation of private and public laboratories and commoditisation of pathology services has been associated with reductions in research activities, career opportunities, and professional pathology input into laboratory management and clinical consultation.

The future history may require a new definition of diagnostic pathology that embraces other fields such as dynamic metabolism, molecular biology and diagnostic imaging, that reinforces the clinical science, and that re-establishes a closer relation with clinical medicine and surgery.

S17: BACK TO BASICS – BUFFERS AND STAINS

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In this presentation we will go “back to basics” and discuss Percentage, Molar and Normal solutions before defining what is a buffer and why they are used.

What is a Buffer? A Buffer is a solution which will resist changes in the concentration of Hydrogen ions in the presence of external and internal influences.
We will then discuss buffers that are commonly used in histological staining, histology stains that require buffers (especially in immunohistochemistry and histochemistry—for example Acid and Alkaline Phosphatase) in order for the stains to work correctly and give optimum results. Examples of such Buffers are Phosphate Buffers, Acetate Buffers and TRIS-HCl. The use of buffers in haematological staining of blood films is pH dependent so a Phosphate Buffer of pH 6.4 is essential for the correct staining of the granules in the white cells.

S18: MORPHOLOGY – CAN WE STILL LEARN FROM THE BLOOD FILM?
B. Bain
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Introduction: The advances in the technology of automated full blood counts means that automated instruments can now do much that was previously done by visual inspection of a blood film. The increasing costs of medical care also mean that there are economic arguments favouring keeping the making and examining of blood films to a minimum. This raises the question of whether there is still important information to be gained from a blood film.

Observations: The observations that will be made are based on the speaker’s 40 year’s experience of laboratory and clinical haematology rather than on published studies. Illustrations of the potential values of a blood film er’s 40 year’s experience of laboratory and clinical haematology rather than previously done by visual inspection of a blood film. The increasing costs of medical care also mean that there are economic arguments favouring keeping the making and examining of blood films to a minimum. This raises the question of whether there is still important information to be gained from a blood film.

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Abnormalities that may be observed in leukemias include an increase of a particular cell population, abnormally homogeneous expression of antigens, abnormally increased or decreased antigens expressed at a particular stage of development, asynchronous antigen expression and aberrant expression of antigens.

Methods: The normal maturation sequence of a range of antigens will be shown and compared to that of a range of conditions involving myeloid cells.

Results: CD34 and CD117 are co-ordinately expressed at the blast stage with early blasts being CD34 negative. CD33 and CD35 are gradually acquired at blast stage. CD14 is found on mature monocytes whereas CD64 occurs on both monocytes and promonocytes. CD16 is a useful granulocyte marker. Acute promyelocytic leukemia has an expanded CD117, CD53 high, CD34 negative and HLDR negative population. A myeloid leukemia with an unusual CD117 high blast population and aberrant expression on CD4 is presented. Acute leukemias with monocytic differentiation display expanded CD64 positive, CD14 negative populations.

Conclusions: Flowcytometry has established itself as a useful supplementary technique in establishing lineage of acute myeloid leukemias. Future applications include detection of minimal residual disease in following treatment of leukemias.

S21: ANTIMICROBIAL SUSCEPTIBILITY TESTING – AN UPDATE
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This presentation will examine recent changes in the antimicrobial resistance profiles of clinical isolates and discuss their detection in the clinical bacteriology laboratory. Emerging antimicrobial resistance mechanisms and their detection in the laboratory will be reviewed for the following organisms—Methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant Enterococcus (VRE) and multi resistant gram negative bacteria producing Extended Spectrum beta-lactamases (ESBL) and carbapenases. Detection methods will include disk diffusion, Vitek automated identification and the application of new chromogenic media for the detection of MRSA and VRE. The possible change to EUCAST methods will also be discussed.

S22: SPECIMEN PREPARATION, ANTIBODIES AND ARTEFACTS IN IMMUNOCYTOCHEMISTRY
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Almost all life scientists will come across the light/fluorescence microscope at some stage, whether to see if the tissues and/or cells are viable or what they look like. Cell biologists, histologists and pathologists are usually interested in the subcellular localization of macromolecules by microscopy (G. Cox, Optical Techniques in Cell Biology, CRC Press 2007, 268 pp).

Methods: Several techniques, both old and new exist, such as cytochemistry, histochemistry, autoradiography, enzyme cytochemistry, in situ hybridization, immunocytochemistry and immunofluorescence. Sample preparation is required for whatever the technique that is being used. In this presentation we will provide a detailed outline of the standard good practice to obtain state-of-the-art immunolabelled samples for ultrastructural assessment. Common occurring artefacts will be approached and illustrated with practical examples.

Results: A lecturer can only introduce the interested life scientist to the pitfalls of sample preparation techniques and hopefully transplant his or her knowledge towards the audience. This presentation aims to provide the scientist with some “unwritten” rules, notes and tricks to train the scientist’s eyes for microscopic details and sample preparation artefacts by the aid of various practical examples.

Conclusions: In conclusion, if you are just starting out, or you just want to refresh your knowledge the best things to do, apart from finding someone who has already worked out what to do with your system, is to attend this seminar and/or to read some literature and pick out a protocol to try as a
Malignant melanoma (melanoma) is the most aggressive and life-threatening of cutaneous malignancies. It develops from melanocytes, the pigment cells found in the epidermis of the skin. The most significant environmental factor associated with the pathogenesis of skin cancer is prolonged exposure to the sun particularly in childhood.

Australia has the highest incidence of melanoma in the world, with over 2100 people in Victoria alone and nearly 10,000 overall being diagnosed with melanoma every year. About half of melanomas are detected by the patient as a new and/ or changing lesion. Doctors detect melanomas either during the course of health examination for other purposes, or in a skin examination to detect skin cancer. Following detection, lesions suspected of being melanoma ideally should be completely excised.

The resulting histopathology report on a biopsy of primary cutaneous melanoma should provide the clinician with the information necessary for optimum patient management. In a large private pathology practice in Australia’s second largest city, approximately 50% of all specimens received in the histopathology department are skin biopsies. These are formalin-fixed and paraffin-embedded according to skin-specific protocols for sample selection, embedding and sectioning. Where indicated, specialised staining techniques including IHC are performed.

Biomedical Scientist (Medical laboratory Scientists) participation in examination and dissection (cut-up) of surgical pathology specimens has a chequered history in the UK. Pathologist support has been diverse over the past 20 years, with a tendency to polarise opinion, especially around the role of the advanced, non-medical, “pathologist assistant” is well developed.

A report published by a joint working party of the RCPath and Institute of Biomedical Science (IBMS) in January 2004 outlined a review of the development of team-work within the laboratory. The role of the medical scientist in the Pathology Team plays a crucial role. The RCPath/IBMS introduced a training logbook and dissection examination and dissection (cut-up) of surgical pathology specimens has a chequered history in the UK. Pathologist support has been diverse over the past 20 years, with a tendency to polarise opinion, especially around the role of the advanced, non-medical, “pathologist assistant” is well developed.

The APC of Coag presentation will provide a back to basics approach to troubleshooting results in a routine diagnostic coagulation laboratory. The AP will cover many aspects of the activated partial thromboplastin time (APTT, "A"), prothrombin time (PT, "P") and clot curve data and error flags ("C"). The impact of various pre-analytical variables and time scenarios on result interpretation and subsequent troubleshooting procedures will be discussed. In addition, the utility of optical coagulation analyser clot curve data as well as the mechanical endpoint analyser error flags will be covered. Real-life examples will be used to highlight various basic result patterns associated with different clinical scenarios and how a knowledge of these patterns and utilisation of all available information, provides a good foundation for developing troubleshooting skills.
To perform their function neutrophils migrate to the site of infection or inflammation, phagocytose foreign microorganisms and go on to destroy them by the activation of the microbialidal arsenal. There are three functional neutrophil phenotypes: (i) quiescent or resting, (ii) primed - when the neutrophils response to an activating agent is potentiated and (iii) activated. Examples of neutrophil priming agents include G-CSF, GM-CSF, LPS, PAF and TNFα, and of activating agents include leukocyte antibodies and FMLP. Neutrophils which are activated after being primed produce an augmented microbialidal response. This indicates that primed neutrophils are a key control point for neutrophil function.

In any response, ideally the magnitude of the neutrophil response would be adequate to deal with the infection or inflammation. However, if the response is excessive or uncontrolled, this may result in injury to the surrounding tissue. This lecture will discuss neutrophil migration, phenotypes and microbialidal response and briefly review immune neutropenias and TRAIL.

S33: MEMORY B-CELLS - DETECTION OF B-CELL MATURATION DEFECTS IN CVID
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Introduction: Common variable immunodeficiency (CVID) is a clinically heterogeneous group of primary antibody immunodeficiency states characterised by impaired immunoglobulin production (especially low levels of IgG and IgA). This is mainly due to impaired B-cell differentiation into antibody forming cells and manifests clinically by increased frequency of upper and lower respiratory tract infections. IgG production is predominately dependent on the presence of isotype switched memory B-cells. Recently, classification of human B-cells in peripheral blood has identified naïve (IgD+/CD27-) B-cells, non-switched memory (IgD+/ CD27+) B-cells (producing IgM, IgG and IgA). CVID patients typically exhibit reduction of memory (CD27+) and isotype switched memory (CD27+/IgD+) B-cells (producing IgM, IgG and IgA). CVID patients typically exhibit reduction of memory (CD27+) and isotype switched memory (CD27+/IgD+) B-cells and may exhibit an increased proportion of immature (CD21-) B-cells. Flow cytometric subclassification helps to identify patients with specific clinical manifestations, particularly lymphoproliferation and autoimmune cytopenias in those with impaired B-cell maturation and isotype switching.

Method: Peripheral blood mononuclear cells (PBMCs) from CVID patients and a control subject were prepared using whole blood / lysate method (CVID (n=36) controls (n=52)). The PBMCs were incubated with a panel of monoclonal antibodies bound to specific determinants on the cell surface detected by a multicolour flow cytometry using FACSCanto II. The analysis was done using FCS Express Software and allowed identification and enumeration of total B-cells (CD19+), memory (CD27+), isotype switched (IgD-/CD27+), immature (CD21-) B-cells and transitional B-cells (CD38+ strong IgM+).

Results: This method allows for differentiation between mature and immature B-cells, total memory B-cells, non-switched and isotype switched B-cells and transitional B-cells.

Conclusions: Enumeration of memory B-cells provides useful information
to guide the clinician in the classification and long-term management of CVID patients. Expansion of immature B-cells has been linked with an increased incidence of splenomegaly. An expansion of non-switched memory B-cells indicates a block at IgM producing stage giving rise to splenomegaly. A severe reduction in isotype switched memory B-cells indicates defective germinal centre development and a higher risk of splenomegaly and granulomatous disease. Expansion of transitional B-cells is significantly linked with lymphadenopathy.


S34: FLOW CYTOMETRY IN THE SCREENING FOR AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) AND X-LINKED AGAMMAGLOBULINEMIA (XLA)

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Introduction: Primary Immunodeficiency Diseases (PID) are rare conditions where inherited genetic defects predispose individuals to an increased risk of infection. Genetic sequencing plays a vital role in the diagnosis of PID but results can often take months. In PID, an early diagnosis and early treatment can reduce the risk of complications arising from infection. Does Flow Cytometry have the potential to deliver results in a comparatively cost effective and timely manner?

Methods: ALPS and XLA were investigated. In both studies healthy donor bloods were stained, lysed and fixed with monoclonal antibodies and reagents supplied by BD. Cells were analysed with BD FACSante II Flow Cytometer and results evaluated by FCS Express software.

Results: ALPS is characterised by the expansion of a normally rare T-cell subset with a unique immunophenotype (CD4+/CD3+/CD4-/CD8-) which can be quantified by Flow Cytometry. XLA is caused by a defect in the Bruton's Tyrosine Kinase (Btk) gene resulting in an arrest of B-cell maturation and proliferation. Analysis of Btk in monocytes by Flow Cytometry can demonstrate the normal (presence) or abnormal (absence or bimodal) expression in suspected XLA patients and family members.

Conclusions: Flow Cytometry is used to screen for ALPS and XLA throughout the world but is not yet widely available within Australia. The results of this investigation are promising. Two new Flow Cytometry methods have been developed and implemented for routine use within the Immunobiology Laboratory, Pathology Queensland, Royal Brisbane and Woman's Hospital. Along with clinical observations and other laboratory findings Flow Cytometry provides supporting evidence for the diagnosis of ALPS and XLA, enabling treatment to begin without waiting for sequencing results.

S35: HEPATITIS B – HISTORY AND OVERVIEW OF HBV TESTING IN AUSTRALIA

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Hepatitis B infection was first identified in 1885 and was known as serum hepatitis, due to its spread via body fluids. The virus was not identified until 1965 when Blumberg discovered Australia antigen, now known as Hepatitis B surface antigen (HBsAg). The virus particle itself was identified by Dane in 1970, using electron microscopy.

Testing for HBsAg was introduced commercially in the early 1970's as a manual haemagglutination method. This was followed by more sensitive radio immunoassay methods and enzyme immunoassays. Since 1980, there has been a rapid development of more sensitive automated assays, including the EIA assays using chemiluminescent signal detection systems.

Hepatitis B is a world-wide public health problem with more than 350 million people infected. Most of these are acquired through perinatal (mother to child) transmission, however Hepatitis B is also acquired through sexual intercourse and IV Drug use. The incubation period is 45-180 days. Approximately 90% of infected adults will have an uncomplicated acute infection where HBsAg and HBV DNA persist for a short period after which there is seroconversion to anti-HBs. Of those infected with HBV, 5-10% of adults will develop chronic infection, where HBsAg may persist for many years. Approximately 30% of children and 90% of infants will develop chronic infection. Hepatitis B surface antigen is produced far in excess of the needs for assembly of virus which makes HBsAg a good marker of HBV infection. HBsAg is produced during viral replication and is used as a measure of active replication and infectivity. Although HB core Ag is only found in the hepatocytes, there is a transient anti-HB core IgM presence in the serum very early in the infection. This is followed by anti-HB core IgG which generally remains positive for life.

The complexity of HBV serology is a challenge even for experienced serologists. With the appearance of variant and mutant varieties of hepatitis B virus, the presentation of serological profiles is varied. Also the advent of treatment with anti-viral drugs presents difficulties of emerging resistance. This seminar will report on a number if clinical case reports on patients and describe the dilemmas provided by atypical results and profiles encountered in the diagnostic laboratory.

S36: A COOK'S TOUR OF TUMOUR MARKERS

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Tumour markers in general are either oncofoetal or functional proteins including hormones which are produced by neoplastic tissue. The clinical uses for tumour markers include: screening; diagnosis/case finding; staging/prognosis; detecting recurrence; and monitoring of therapy. Tumour markers are often misused as tools for screening malignancy e.g. PSA is not recommended for prostate cancer screening but is recommended for recurrence and monitoring of disease. It is important to note that tumour markers currently in use are not organs or tissue specific and are not clinically specific or sensitive for malignancy. Tumour markers and the tissue or organs associated with their clinical use include: liver (AFP, CEA, ferritin); breast (CA 15-3, CEA); colon/rectum (CEA, CA 19-9); prostate (PSA, free PSA, PCA3); testis (hCG, AFP, LD); ovary (CA 125, HE4, CA 72-4, AMH, Inhibin B); pancreas (CA-19-9, CEA); thyroid (calcitonin, thyroglobulin); pituitary (prolactin, GH/IGF-1, ACTH); neuroendocrine (serotonin, 5HIAA, chromogranin A, metanephrines); lung (NSE, SCC, CEA, mesothelin); melanoma (S-100); cervix/uterus (SCC, CEA); and blood (protein EPG/IIE, free light chains, ß2-microglobulin). Combinations of tumour markers are now being used to improve diagnostic sensitivity and specificity e.g. CA125, HE4 and CA 72-4 in ovarian cancer. Many tumour markers are measured by immunoassay techniques and interferences such as heterophilic antibodies and the hook effect must be considered when discordant results are observed.

S37: FREQUENCY OF GP.MUR IN AN AUSTRALIAN DONOR POPULATION

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Introduction: GP.Mur is a hybrid glycoporphin expressed on red blood cells. Antibodies to neoantigens (Mur, Mur, and Hil) found on GP.Mur can cause haemolytic transfusion reaction and haemolytic disease of the foetus and newborn. GP.Mur is found in 5-8% in East Asian populations. Over 8% of the Australian population are of Asian ethnicity however, there are no reports of GP.Mur frequency in the Australian blood donor population. The aim of the study was to establish a high resolution melt (HRM) genotyping method to assess the frequency of GP.Mur in the Australian donor population.

Methods: Standard serological procedures were performed using monoclonal antibodies (Mi, III, Mur, and Mia) and polyclonal anti-Hi to GP.Mur neoantigens. Using primers from previously published method, PCR was performed using HRM kit (QIAGEN). DNA from donors that were serology-positive (n=13) and serology-negative (n=10) for GP.Mur were investigated to validate HRM genotyping. One hundred donors were selected from collections by Donor Mobile units at locations with a high frequency of blood donors of East Asian background. All samples were serotyped and genotyped.

Results: HRM genotyping showed 100% concordance with serology. GP.Mur was detected in 3 out of 100 donor samples by both serology and genotyping.
**S39: REVIEW OF TECHNIQUES USED IN THE R.C.P.A TRANSFUSION Q.A.P. SURVEY**

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**Introduction:** For 2009 the R.C.P.A. blood bank quality assurance program went from paper to online result entry. Registrants recorded their methods and techniques against a comprehensive list of reagents, manufacturers and technologies, which have been kept in a database. The focus of the survey results has been around expected reaction strengths and interpretation based on methods but there has been no report on the method mix and the percentage of labs that have automated their testing. Significant changes in methodology mean very few laboratories now use tubes preferentially. Columns within column technology there are however differences between gel and glass beads. We will analyse, and present these differences.

**Conclusion:** Findings from these two cases support evidence from literature on certain characteristics that may be associated with increased haemolytic reactions after IVIG infusion. These include high-cumulative-dose IVIG therapy to non-blood group O individuals; and presence of an underlying inflammatory condition in the two cases.

**S40: WOULD YOU LIKE BUGS WITH THAT? STRATEGIES IN THE PREVENTION OF TRANSFUSION TRANSMITTED INFECTIONS**

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**Introduction:** What is the world’s best practice in the prevention of infection when receiving blood components? Can 100% safety ever be guaranteed and at what cost? A review of strategies to prevent transfusion-associated infection around the world will showcase world’s best.

**Method:** A literature review was conducted to analyse the various methods employed globally to prevent pathogen transmission via blood components. Efficacy, wastage and cost of the strategies were analysed and compared.

**Results:** Donor selection utilising volunteer donors and medical questionnaires do increase safety, but remove potentially healthy donors from providing blood. Collection strategies, including skin swabbing and diversion pouches are cost-effective ways to reduce the chance of bacterial contamination. Pathogen screening using serology and Nucelcid Acid Testing significantly reduces the threat of infection (but only for the pathogens screened for), have wastage from biological false positives and still leave a window period of residual risk. Bacterial screening of platelets can remove contaminated units before they are transfused, however many are transfused before results are known and there is wastage from biological false positives. Quarantine Fresh Frozen Plasma removes the risk of the window period, but only for the pathogens tested for and is very resource expensive. Pathogen inactivation closes window periods, is effective against known, unknown, emerging and re-emerging pathogens and failed screening tests, mitigates cost by eliminating some tests and processes and increases supply of extended expiry components.

**Conclusion:** It has been shown that a combination of suitable donor selection, collection, pathogen screening and pathogen inactivation strategies gives the safest result for the money spent. Pathogen inactivation changes the paradigm and will force us to rethink our current strategy.

**S41: MICROARRAY TESTING / GENE ANALYSIS**

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The completion of the human genome project has enabled major advances in the field of molecular pathology culminating with the ability to identify new therapeutic targets and biomarkers in cancer. Key technologies responsible for these advances include microarray-based gene expression profiling, functional genomics, high-throughput genetic profiling by single nucleotide polymorphism (SNP) analysis, tissue microarray (TMA) technology, digital slide scanning, computerised image analysis and more recently, next generation sequencing. Microarray testing has been used to aid in the classification of tumours into molecular subtypes enabling more accurate patient prognosis. Massively parallel sequencing or next generation sequencing (NGS) allows for rapid sequencing of small fragments of DNA or RNA with mapping back to a reference genome. It offers the potential to classify patients into subpopulations that differ in their response to a specific treatment. The current status and future possibilities of these technologies will be discussed.

**S42: NEW BIOMICROSCOPIC MICROSCOPY AND RELATED CORRELATIVE IMAGING TOOLS TO DISSECT CELLULAR STRUCTURE AND FUNCTION (IN HEPATIC COLORECTAL ME-TASTASIS)**

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**Introduction:** To genuinely understand how complex biological structures function, we must integrate knowledge of their dynamic behaviour and of their molecular-level structural machinery (Braet et al. J Cell Mol Med 2007;11:759-763). The combined use of light-, laser-, and/or electron microscope techniques has become increasingly important in our understanding of the structure and function of cells and tissues at the molecular level. Such a combination of two or more different microscopy tech-
Methods: CM allows to gain additional novel structural-functional information and this provides a degree of confidence about the structures of interest as information obtained with one method can be compared to that seen with the other methods. This is the strength of CM especially when it is combined with combinatorial and/or non-combinatorial labelling approaches (Braet et al. Microsc Res Techniq 2007:70;230-242).

Results: In this contribution, we will present different combined and correlative high-resolution imaging methodologies and how these microscopy techniques facilitated the accumulation of new insights in the morpho-functional and structural aspects of colorectal cancer. Various aspects of hepatic colorectal metastases regarding the molecular dynamics and inter- & intracellular signalling will be explored throughout this presentation by comparing the results of confocal laser scanning-, corelative fluorescence & scanning electron-, atomic force- and whole-mount electron micros copy.

Conclusions: By drawing on these novel structural and mechanistic understanding my team and collaborators are designing and assessing new strategic therapeutic approaches for the treatment of cancer. Key approaches under current investigation are (i) hydrogel-based carriers for sustained, local application of anti-cancer drugs and (ii) metal-based nanoparticles, such as iron-gold complexes, that show selective activity towards cancer cells.

S43: BONE HISTOMORPHOMETRY: APPLICATION AND TECHNOLOGIES
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Introduction: Bone histomorphometry is the microscopic analysis of the morphology and organisation of bone tissue. It is commonly used to evaluate metabolic changes in bone tissues including changes in bone density, structural reorganisation of the bone matrix, as well as dynamic measurements of bone formation and bone resorption activities. While there are a number of current methodologies to measure bone density, strength of bone tissue is determined not only by mass but also by architecture. The organisation of the bone matrix bestows significant mechanical strength which needs to be considered together with material properties of the bone to understand a patient’s bone health. Densitometry is still the gold standard used to diagnose osteoporosis status; however it is limited in its ability to assess morphological aspects of bone tissue, relying solely on the inorganic mineral phase.

Therefore, the use of histomorphometry to assess bone health can improve calculation of fracture risk and provide a more accurate assessment of metabolic bone states.

Methods: Currently two major technologies are used to study bone histomorphometry: tissue histology and computer tomography (CT). Advantages of CT include non-invasive approach, speed of analysis and ability to generate volumetric data; and advantages of histology include ability to measure dynamic changes in the bone matrix dependent on cellular activity such as bone formation rates and resorption activity and analysis of molecular expression patterns. Histological analysis of bone tissue can be performed on decalcified paraffin sections or for the purposes of dynamic bone histomorphometry non-decalcified resin sections. The activity of the bone-nerosorbing osteoclasts is determined by measuring the proportion of bone surface undergoing resorption. In addition, the activity of bone-forming osteoblasts is measured through the use of fluorochrome labels which are calcium-binding substances that are preferentially taken up at the site of active mineralisation. In rodent models, two labels are administered intraperitoneally at 7 and 2 days before animal sacrifice, with the distance between the labels indicating the proportion of new bone deposited within a 5 day period allowing calculation of the rate of bone formation.

Results: MicroCT analysis of fracture healing and bone metastasis in mouse models allows measurement of bone density, bone volume and architectural variables such as trabecular thickness, number and separation.

Tissue histology of fracture healing and bone metastasis in mouse models allows measurement of bone area, architectural variables such as trabecular thickness, number and separation, mineralising surface, mineral apposition rate, bone formation rate, resorption surface and immunohistochemical analysis of cellular populations and gene expression.

Conclusions: Bone histomorphometry provides extensive analysis opportunities in the monitoring and evaluation of bone tissue and is well established in the research community. It has the potential to enhance clinical analysis of bone tissue quality in patients.

S44: WORKFORCE AND CAREER DEVELOPMENT
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Introduction: 49% of Health Sector employees are looking to leave their jobs. Organisations are asking the right questions. How do we retain and develop talented and skilled staff?

Content: Organisations need to get it right the first time. Fit the right person to the right job, pay well and have strong leaders. Promote from within and encourage skill development. Organisations need to look after what they have, nurture their assets, retain their skilled and knowledgeable staff and be creative with their career development opportunities. Organisations need to invest in their staff, build basic people management skills, add value through staff skills and identify barriers to better performance.

Conclusion: Organisations need to provide overall strategic direction for Workforce and Career Development.

S45: LEARNING, COMPETENCY, ACCREDITATION = LIGHTS, CAMERA, ACTION
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In September 2004 the Health Practitioners Competency Assurance Bill (2003) came into force in New Zealand. This required all Practicing Health Professionals in the country to demonstrate evidence of competence to practise as a professional and to hold an Annual Practising Certificate (APC).

To be eligible for an APC, the Medical Laboratory Science Board (MLSB), the government regulatory body, required all scientists, scientific officers and technicians to participate in, and demonstrate performance in an approved recertification programme.

The New Zealand Institute of Medical laboratory Science (NZIMLS) developed a Competency and Professional Development (CPD) Recertification Programme which was accredited by the MLSB for this purpose.

This presentation will look at the performance of that CPD recertification programme over the past six years: its development, successes and failures, audits, practitioner response and the people involved.

‘The Good, The Bad and The Ugly.’

S46: ARE WE OVER-TRAINING? SHOULD OUR PROFESSION CONSIDER A NEW MODEL OF UNIVERSITY QUALIFICATION FOR MEDICAL (LABORATORY) SCIENTISTS?
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In New Zealand the Bachelor of Medical Laboratory Science has been offered since 1994 from three universities, with a similar structure throughout the 4 years of the course. This 4-year structure is viewed as valuable but is expensive. In particular the cost of the clinical placement which occurs in the 4th year is costly both to laboratories that provide this clinical placement and to the universities. While academically and professionally sound, the universities are all mindful of the cost of this 4th year.

Many courses as well as the New Zealand degree programmes require students to study two of the disciplines in Medical Laboratory Science to a higher level.

A survey is planned for representative areas of the staff of New Zealand
Labsory to see how many of the scientists have practiced in both of the disciplines that they qualified in. The results would lead to a discussion within the profession regarding the structure of the degree. It will be of interest and significance to members of the profession, the Professional bodies that represent them, the Registry Authorities, and to the Universities that offer qualifications for the Profession.

S47: THE ROLE OF EXTERNAL QUALITY assured in IDENTIFYING LABORATORY PERFORMANCE
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Introduction: As part of its continual assessment and monitoring program to increase the competency of pathology laboratories and patient safety, Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs Pty Ltd (QAP) sought funding from the Department of Health and Aging for the Role of External Quality Assurance in Identifying Poor Performing Laboratories. Previously the RCPA QAP ran a Key Performance Indicator (KPI) trial.

Methods: The previous Chemical Pathology KPI trial has been revisited and KPIs are being developed for other disciplines, notably Anatomical Pathology, Cytopathology and Transfusion Serology. Cumulative KPI data is being reviewed to set benchmarks for each KPI discipline.

Results: The trials will determine whether early indicators of performance can be developed around the regular EQA that laboratories perform as part of the accreditation process.

Conclusions: Initial indications from trials are promising.

S48: EXTREME SNAKEOVER
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Since 1930, CSL Ltd has developed, manufactured and marketed a range of snake, spider and marine antivenoms. With over 800 people each year hospitalised due to snakebite and an average of 2-4 fatalities, these Products of National Significance are vital in the treatment of the envenomed patient to prevent severe morbidity or mortality.

Since the inception of this unique product range, a number of product and manufacturing improvements have been implemented to ensure compliance with strict regulatory requirements, continued safety, efficacy, specificity and optimum use. Furthermore, contributions to worldwide improvement in the treatment of snakebite victims have been high on the agenda.

Improvement projects, many requiring significant capital investment, have included improved quality control with the introduction and/or update of analytical assays for the antivenom range; introduction of viral contamination testing by PCR analysis; filtration improvements optimising purity and maximum volume of the end Immunoglobin concentrate.

Corporate Responsibility initiatives have also seen CSL contribute to the WHO worldwide Standardisation of Antivenom Production and Control Project.

CSL is the sole manufacturer of Antivenoms for human use in Australia and continuously implements product improvements that will contribute to best patient outcomes and improve snakebite education on a National and International scale. Optimum treatment of the envenomed patient is the ultimate aim.

S49: NEW DEVELOPMENTS IN LC/MS/MS FRONT-END AUTOMATION
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The selectivity and sensitivity of LC/MS/MS offers the potential for more reliable measurement compared to other detection systems, such as immunoassays. Despite a number of challenges, clinical applications are the fastest growing area today for LC/MS/MS. The demands for increased efficiency, reduced turn-around time and equipment utilisation have been some of the major drivers to automate LC/MS/MS procedures. These include sample preparation and multiple parallel LC system inlets (Multiplexing). Pre-analytical sample preparation is a necessity in LC/MS/MS. The removal of matrix components that foul the analytical column leading to column failure and components that cause ion suppression is crucial for trouble free chromatography.

Solid Phase Extraction (SPE) is widely recognized as one of the most efficient sample preparation procedures. The benefits include lower sample volumes, cleaner extracts and reduced ion suppression issues. The use of SPE also allows the utilisation of automation, leading to reduced sample handling, simplified SPE protocols and parallel sample processing.

Multiple parallel LC system inlets (Multiplexing) accelerate sample throughput by up to 4 times leading to enhanced productivity and improved equipment utilisation. Mass Spec idle time is reduced to a minimum.

This presentation will cover a number of new LC/MS/MS front-end automation sample cleanup options that are available along with the use of multiplexing. Practical examples of their use in a clinical environment will be shown along with their benefits to the laboratory.

S50: HAEMOGLOBINOPATHIES IN THE DIAGNOSTIC LABORATORY
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Introduction: The diagnostic haematology laboratory needs to consider the purpose of screening or testing for haemoglobinopathies, the technology that is most appropriate and how the results should be interpreted.

Observations: Testing for a haemoglobinopathy may be performed to elucidate the nature of a clinical or diagnostic problem such as (i) clinical features suggestive of sickle cell disease or thalassaemia major or intermedia (ii) clinical or laboratory features suggestive of haemolytic anaemia (iii) unexplained polycythaemia (iv) unexplained cyanosis (v) unexplained microcytosis. Screening may be (i) to confirm or exclude the presence of haemoglobin S preoperatively (ii) to detect possible sickle cell disease in a neonate (iii) to detect abnormalities in potential parents that may lead to serious disease in offspring. The methods employed will depend on cost, convenience, workload, speed with which results are needed and the nature of the sample available. As a primary method, high performance liquid chromatography (HPLC) is steadily replacing haemoglobin electrophoresis. The role of capillary electrophoresis as a primary method is not yet clearly defined.

Conclusions: In multiracial communities, such as much of Australia, haemoglobinopathy diagnosis and screening is now a significant part of the workload of haematology laboratories. Methods and training must be appropriate for the needs of the community.

S51: GENE EXPRESSION ANALYSIS OF SQUAMOUS CELL CARCINOMA OF THE OESOPHAGUS USING A NOVEL REAL TIME PCR PROBE SYSTEM
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Introduction: Squamous cell carcinoma of the oesophagus (OSCC) is a common malignancy that occurs with high frequency in certain parts of the world, including South Africa. Recent reports implicate a variety of genetic factors in the carcinogenesis of OSCC but their involvement is yet to be defined.

Purpose: The objective of this study was to examine the significance of the relative gene expression of VEGF, HER1, HER2 and MMP2 genes in oesophageal squamous cell carcinoma (OSCC).

Methods: We used a novel quantitative real time PCR universal probe-
say to measure the mRNA levels of VEGF, HER1, HER2 and MMP2 genes in a cohort of individuals with OSCC in Durban, South Africa. The mRNA transcript levels of these genes were also correlated with each other to indicate any expression relationship. The correlation of VEGF, HER1, HER2 and MMP2 gene expression with clinicopathological features was investigated as well as the correlation of clinicopathologic factors with each other.

**Results:** The mRNA levels of VEGF, HER1, HER2 and MMP2 genes were higher in squamous cell carcinomas (SCCs) than in normal oesophageal tissue. Squamous cell carcinomas expressed significantly higher levels of HER1 (p = 0.002). Correlation analyses of mRNA levels of the VEGF, HER1 and MMP2 genes in oesophageal tumours showed that VEGF was associated with MMP2 by 79.8% and with HER1 by 86.4% and HER1 was associated with MMP2 by 88.8%. There was a significant correlation of increased mRNA levels of VEGF in male patients (p = 0.044). A larger tumour size was associated with an increased mitotic rate (p = 0.043) and increased necrosis (p = 0.043). Anaplasia was associated with an increased depth of tumour invasion (p = 0.015).

**Conclusions:** The overexpression of VEGF, HER1, HER2 and MMP2 genes in oesophageal tumours implicates a possible role in both the tumourigenesis of OSCC and the pathophysiology of tumour growth and spread. The positive correlations between clinicopathological factors, such as gender and race, to gene expression suggest a multi-factorial aetiology of OSCC. Further large scale and in-depth gene expression studies, combined with clinicopathological analyses are necessary for a better understanding of OSCC carcinogenesis.

**S52: MOLAR PREGNANCY – MOLECULAR TECHNIQUES**

R. Lourie, M. Williams

Hydatidiform moles (HM) are uncommon abnormalities of placental villous tissue which carry a risk of persistent gestational trophoblastic disease, including choriocarcinoma. Distinction of HM from non-molar (NM) products of conception, and sub-classification of HMs as complete hydatidiform mole (CHM) or partial hydatidiform mole (PHM), are important in clinical practice as risk of persistent gestational trophoblastic disease and clinical management differs for CHMs, PHMs, and NMs. Morphological examination alone shows poor interobserver reproducibility, particularly in the diagnosis of PHM, leading to both under diagnosis, and unnecessary follow up for patients with NM miscarriages. The unique genetic features of CHMs, PHMs, and NMs can be exploited to improve diagnosis of HMs. CHMs have diandric, diploid, paternal-only genomes that are usually homozygous (46XX diploid karyotypes arising from fertilisation of an empty egg by 1 spermatozoon followed by duplication; 90%), or heterozygous (46XX or 46XY karyotypes arising from simultaneous fertilisation of an empty egg by 2 spermatozoa; 10%). PHMs are triploid with a diandric, monogenic genome arising from fertilisation of a normal egg by either 2 heterozygous spermatozoa (heterozygous; 90%) or 1 spermatozo-on with duplication (homozygous; 10%). Using a commercial forensic short tandem repeat DNA genotyping assay (Applied Biosystems Identifier Plus), the genetic basis of potentially re-molar products of conception can be characterised from formalin fixed, paraffin embedded, tissue. HM can be sub-typed as CHM or PHM, with CHMs demonstrating exclusively paternal alleles at all loci, and PHMs demonstrating 2 distinct paternal alleles in at least 2 loci, allowing appropriate clinical surveillance. HM can be excluded in NM pregnancies, including digynic, nonmolar triploid pregnancies, releasing these patients from extended follow up.

**S53: HITTS: A DIFFICULT CLINICO-PATHOLOGICAL CORRELATION**

A. Henden

The diagnosis of Heparin Induced Thrombocytopenia Thrombosis Syndrome (HITTS) remains a clinical one, although its occurrence in critically unwell patients and non-specific signs means diagnostic certainty is often lacking. Currently available laboratory tests aim to support the clinical diagnosis however use very different techniques to demonstrate pathogenic antibodies or functional activation of platelets. The current ‘gold standard’ in laboratory diagnosis remains the Serotonin Release Assay (SRA), a complex and time-consuming test, using radioactive serotonin and performed by few laboratories. The clinical basis for diagnosis of HITTS and the role of various laboratory tests, including newer methods to demonstrate platelet activation, will be discussed.

**S54: HITTS AND WHOLE BLOOD IMPEDANCE AGGREGOMETRY**

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**Introduction:** Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin use. IgG antibodies to complexes of platelet factor 4 (PF4) and heparin trigger the clinical manifestations of HIT. Only a subset of these antibodies will activate platelets and these can only be identified with platelet aggregation (functional) assays. Heparin-induced platelet aggregation (HIPA) and 14C-serotonin release (SRA) assays for HIT are time-consuming and complex to perform. The 14C-serotonin release assay (SRA), the gold standard in HIT diagnosis, is highly sensitive but only performed in one Australian laboratory and hence unsuitable for routine use.

**Methods:** We have developed a whole blood impedance aggregometry (WBIA-Multiplate®) and in a small cohort of HIT-antibody positive patients, patients have shown it to be superior to light transmission aggregometry and as sensitive as the SRA. We have used WBIA and SRA to test 181 samples positive for H-PF4 antibodies by PaGIA or ELISA We obtained ethics approval to conduct a multi-centre study to validate the WBIA as a suitable diagnostic tool in HIT.

**Results:** Using a selected donor (high responder), 77 samples were positive by WBIA (aggregation with low dose 0.5IU/ml H but not with high dose). SRA was performed using the same donor platelets, serotonin was released from 100 samples (>20% release with 0.1IU/ml H) with only 80 true HIT samples (release>20% with 100IU/ml H). Ten samples exhibited discrepant results: 1 strongly positive (89% release) and 6 weakly positive by SRA (average release 56%, range 22-74%) were WBIA negative. These 7 samples were retested using a random donor, only 2 remained SRA positive. Three samples were SRA negative but strongly WBIA positive.

**Conclusion:** In this multi-centre study, with a selected high responder donor, WBIA had a sensitivity of 91.3% which could rise to 97.3% using random donors for SRA, a specificity of 96.1% and a PPV of 94.8%. WBIA is easy to perform with rapid turn-around time and warrants further investigation as confirmatory assay for platelet-activating HIT antibodies.
Also in this context, other DNA sequence variants, commonly regarded as benign polymorphisms may influence CFTR function, supporting the view that CF is a “spectrum disorder” rather than an absolute diagnosis. Diagnosis of CF in adults requires appropriate clinical awareness; interpretation of both sweat testing and full CFTR gene sequence data.

S56: SPECIFIC IGE SENSITISATION IN A SIX-YEAR OLD INFANT COHORT IN NEW ZEALAND

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Introduction: The aim of the study was to determine sensitisation to inhalant and food allergens in 6-year old children in New Zealand.

Methods: Specific IgE (sIgE) levels were determined to 12 inhalant and food allergens in 659 6-year old children from Wellington (n=316) and Christchurch (n=343) from a birth cohort. sIgE was measured by a 3rd generation liquid chemiluminescent enzyme immunoassay (Siemens IMULITE 2000). Atopic sensitisation was defined as at least one sIgE ≥ 0.35 kU/L. Results are presented as proportions and geometric means with 95% confidence intervals.

Results: Sensitisation was present in 299 children (45.4%). Sensitisation to D. pteronyssinus was most prevalent with 176 children sensitised (26.7%) and with the highest sIgE levels (geometric mean: 9.1 kU/L; 95% CI: 6.2-13.2; highest level: 3,295 kU/L). Of these 176 children, 128 had a specific IgE activity to D. pteronyssinus ≥ 4%. The next highest sensitisation rate was to rye grass (141 children, 21.4%) followed by egg white (124 children, 18.8%). Mono-sensitisation was observed in 122 children (18.5%). 44 to egg white, 35 to D. pteronyssinus, 18 to rye grass, 6 to cat pelt, 5 to cow’s milk, 4 to peanut, 3 to horse hair, 3 to dog hair, and 1 each to cockroach, A. fumigatus, Alternaria and olive pollen. The other 177 children were poly-sensitised: 60 to two allergens, 40 to three, 26 to four, 22 to five, 17 to six, 3 to seven, 5 to eight, 3 to nine and 1 to all twelve. Of those poly-sensitised the highest sIgE level in three-quarter of these children was to D. pteronyssinus followed by rye grass.

Conclusions: Sensitisation to inhalant and food allergens is high in New Zealand 6-year old children with sensitisation to D. pteronyssinus the most prevalent and with very high sIgE levels and specific IgE activity.

S57: THE EMERGENCE OF A NEW DEFINITIVE TYPE OF SALMONELLA TYPHIMURIUM IN HUMANS AND ANIMALS IN NEW ZEALAND

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Introduction: This paper takes a retrospective view (Camera) on an event that began 5 years ago in New Zealand using traditional as well as novel technologies (Back to basics/Back to the future). In May 2006, a new Salmonella Typhimurium RDNC (reacts with phages but does not conform to a known phage pattern) was confirmed in New Zealand. The pattern was designated DT (Definitive Type) RDNC-May 06. The first isolate was from a 3 year old male from the North Island. By December 2006, DT RDNC-May 06 had been isolated from cows, birds, pigs, cats, horses and more recently from shellfish, lettuce and poultry feed.

Methods: All Salmonella isolates were serotyped using the Kauffmann–White scheme and phage typed using the scheme of Anderson et al. Isolates were further characterised using Pulsed Field Gel Electrophoresis (PFGE) and/or Multiple Loci VNTR Analysis (MLVA).

Results: Cases of DT RDNC-May 06 are distributed throughout the North Island. The first South Island isolate was confirmed in May 2008. Sixty percent of cases are children aged <10 years. In humans DT RDNC-May 06 has demonstrated a peak isolation time in September each year (spring). Molecular typing has been performed on DT RDNC-May 06 isolates and has demonstrated the presence of a dominant PFGE and MLVA profile. In September-October 2010 the number of animal DT RDNC-May 06 showed a significant increase i.e. from 6 in 2009 to 18 in 2010 (September-October).

Conclusion: By the end of 2010 a total of 425 DT RDNC-May 06 isolates have been confirmed by the Enteric Reference Laboratory, of which 264 are from human origin (17 from the South Island).

S58: BACK TO THE FUTURE - UTILIZING AN OLD TECHNOLOGY TO BREAK NEW GROUND IN MICROBIOLOGY

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Introduction: In the past, microbiology has been a reasonably hands-on, non-automated division of Pathology. Recent steps forward in instrumentation include blood culture instruments and automated organism identification and sensitivity testing. Relatively new technology is now on the market in Australia, part of which uses the old technology of Mass Spectrometry, MALDI-TOF (Matrix-Assisted Laser Desorption/Ionisation Time-Of-Flight) instruments are bringing about radical change to organism identification. Microbiology at the Central Laboratory has had the opportunity to trial the validity of implementing this technology into a modern microbiology laboratory.

Methods: Significant isolates which had been identified using the current Vitek2 instrument were also run through the MALDI-TOF. A subset within the MALDI-TOF method of preparation with and without a Formic Acid step was also investigated. Evaluation of current workflow processes was performed to determine the most suitable way to implement this technology.

Results: MALDI-TOF set-up time was seconds, compared to minutes for the Vitek2. Organism identification occurred in minutes rather than 16 to 18 hours. Robust routine pathogenic organisms gave comparable results. The use of Formic acid in the preparation step appears to be beneficial for some Gram positive and mucoid organisms. A change in workflow management accelerated organism identification by up to 24 hours, which is a tremendous improvement for patient treatment.

Conclusion: The rapid, accurate results generated by MALDI-TOF are an exceptional asset to medical microbiology laboratories, decreasing turn around time and therefore speeding up patient management. Implementation would depend on laboratory size and appropriate integration with current workflow processes. This technology could be the future of organism identification and it may become the standard method in microbiology laboratories over the next few years.

S59: COMPETENCY, DO YOU HAVE THE KNOWLEDGE SKILLS AND ABILITIES?

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The presentation identifies the concept of competency assessment from a pragmatic stance. Different aspects will be covered and the topic of 'why you have standards to assess against' is possibly the most controversial as this raises the question of who sets these standards. The presentation continues to consider the elements of competency, what and when do we assess and finally how.

Hopefully you will be convinced that there is a need to assess staff for competency in your laboratory. The question then arises, who should perform competency assessments. Is this you?

S60: TEAM DEVELOPMENT FOR LABORATORY PROFESSIONALS

J. Mcdermott
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S61: TEAM DEVELOPMENT FOR LABORATORY PROFESSIONALS

J. Mcdermott
JoeM@adhb@govt.nz

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tion within the Team and an understanding of how an individual contributes towards the success of the organisation. Conflict resolution will also be discussed.

We will look at examples of extremely successful Teams and discuss how they achieved this status.

We will also explore the concept of motivation. The audience will be invited to discuss some of the problems that Teams throughout the world face on a regular basis.

Finally in summary we can say “Where to from here?”

S61: MESENCHYMAL STROMAL CELLS
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Mesenchymal Stromal Cells (MSCs) are a non-homogeneous population of plastic-adherent cells which were initially isolated from post-natal bone marrow. They have the capacity to differentiate to multiple mesodermal lineages including bone, cartilage and adipose tissue. In stringent culture conditions, MSCs can also be induced to differentiate into different cell types of endoderm and neuroectoderm lineages. To date, no specific marker identifies MSCs, although a number of cell surface antigens have been described which enrich for MSCs. Mesenchymal stromal cells possess a number of properties which has generated a great deal of interest in utilising them in a diverse number of cellular therapeutic applications. The capacity of MSCs to differentiate into multiple different cell lineages has seen them actively explored for tissue repair, particularly in cardiac, orthopaedic and neurological applications. A large body of data indicates that MSCs possess immunomodulatory properties. Mesenchymal stromal cells are immunosuppressive, interacting with T lymphocytes, antigen presenting cells, B lymphocytes, and natural killer cells. In addition, they are immunogenic allowing transplantation across allogeneic barriers. These immunomodulatory properties have seen infusion of MSCs for the treatment of steroid refractory graft-versus-host disease, a life threatening complication of haemopoietic cell transplantation, with promising results. Furthermore these immune functions may lead to roles in the facilitation of engraftment, induction of tolerance and as therapy in autoimmune disease.

S62: CURRENT TRENDS AND NEW INITIATIVES IN POINT-OF-CARE TESTING
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A point-of-care (PoC) test is a pathology testing performed in a clinical setting at the time of patient consultation, generating a test result that is used to make an immediate informed clinical decision regarding patient care. Interest in the field of point-of-care testing (PoCT) has expanded rapidly both within Australia and at a global level, as the array of test profiles, advances in technology and clinical applications continue to evolve.

This workshop will examine some of the technological advances and clinical applications for PoCT in the disciplines of clinical chemistry, haematology, microbiology and infectious diseases, and pharmacology. Selected working examples of Australian and global PoCT field programs being conducted in remote settings, where the challenges of implementing and sustaining PoCT are greatest, will also be presented. Case studies to illustrate the clinical, operational and economic benefits of on-site PoCT will be described. A practical demonstration of several new devices/technologies will also be given.

Education and training of medical scientists and practising health professionals is a crucial component of building a workforce capable of conducting quality-assured community-based PoCT into the future. Selected examples of current education programs on PoCT both within the author’s institution, within Australia and overseas will be discussed.

Professional associations and expert groups have a role to play in advocacy for PoCT and the promulgation of practical, evidence-based guidelines. The role of the AIMS Working Committee on Point of Care Testing for Infectious Diseases and Drugs of Abuse will be reviewed at the Workshop.
P1: PSEUDO HAEMOGLOBIN H PEAK ON HIGH PERFORMANCE LIQUID CHROMATOGRAPHY
J. Duncan

Introduction: Haemoglobin H (Hb H) is seen in association with alpha thalassaemia where the reduction in alpha globin chain production results in a surplus of beta globin chains which form tetramers to produce Hb H. High performance liquid chromatography (HPLC) is widely used in laboratories to quantify Hb A2 and Hb F and as a primary screening tool for the identification of variant haemoglobins. The accurate detection and identification of variant haemoglobins and thalassaemia is best achieved using a combination of techniques.

Our patient presented to the laboratory with a history of rapid onset haemolysis. The blood film and red cell indices were suggestive of oxidative haemolysis with a thalassaemia, possibly Hb H disease, prompting an investigation for thalassaemia.

Methods: HPLC was performed on the Bio-Rad Variant II using the beta thalassaemia short program. After examination of the initial chromatogram the blood sample was washed in saline and repeat HPLC analysis performed.

Results: The HPLC chromatogram showed a sharp peak with a retention time (RT) similar to Hb H. The alkaline electrophoresis and isopropanol stability test were normal and there were no Hb H inclusions. The biochemistry profile showed a markedly raised bilirubin. The washed sample produced a normal HPLC chromatogram.

Conclusions: Interference by bilirubin is common to many chemistry procedures. There are reports in the literature of high levels of bilirubin producing a sharp peak on HPLC with a RT similar to Hb H. This case highlights the importance of secondary confirmatory testing as well as the availability of other haematological and biochemical parameters for the accurate identification and subsequent diagnosis of a variant Hb or thalassaemia.

P2: NOCTURNAL TISSUE HYPOXIA IN OBSTRUCTIVE SLEEP APNOEA ASSESSED BY OVERNIGHT CHANGE IN URINE URATE AND SERUM AMINOTRANSFERASES
S. Hemmady

Introduction: Obstructive sleep apnoea syndrome (OSAS) is associated with diminished arterial oxygen saturation (SaO2) that leads to tissue hypoxia. Traditionally physicians rely on polysomnography for diagnosis. Our study investigates an overnight change in urinary urate to creatinine ratio or aminotransferase that is significantly different between OSAS and healthy subjects.

Methods: Consented patients referred for sleep study at sleep laboratory, Auckland Hospital to be recruited. Demographic details obtained, Pre-bed spot urine and blood collected. First void urine and blood samples collected in the morning immediately after the sleep study. Urine urate, creatinine, plasma urate, creatinine are measured by enzymatic colourimetric and compensated kinetic colourimetric Jaffe method respectively on Roche Hitachi Modular. Aminotransferase levels are measured by enzymatic colourimetric method on the same Modular.
Results: Overnight changes in urate over creatinine and aminotransferase levels were investigated. Results obtained would be compared to results of The Epworth sleepiness scale. Comparison of data for delta urine urate/creatinine ratio and aminotransferase correlating to SaO2 levels and AHI are used to determine the normal group from patients with mild to significant OSAS.

Conclusions: Direction and magnitude of change in urine urate to creatinine ratio and plasma aminotransferase levels before and after sleep could be potential markers of significant overnight tissue hypoxia in OSAS. This would be the first such study in New Zealand to use biochemical markers to predict OSAS.

P3: A COMPARISON OF BLOOD FILM COMMENTS BETWEEN CELLAVISION DM96 AND CONVENTIONAL MICROSCOPY
L. Henshaw

Introduction: The objective of the study was to compare morphological findings between conventional microscopy and CellaVision DM 96. CellaVision is an automated digital cell image analysis system which has the ability to locate and classify white blood cells and photograph areas of red cells on a peripheral blood smear.

Method: Two hundred and nine randomised blood films were examined independently by two experienced morphologists using both conventional microscopy and CellaVision. Films were generated in response to analyser flagging from the Sysmex XE2100 or a clinician's request. Conventional microscopy was considered the "true" value and CellaVision findings were compared to this standard.

Results: Bar graphs were used to compare data. These showed that normal red cells and white cells with toxic changes had good method correlation. RBC changes showed variable correlations depending on the abnormality. Platelet clumps and fibrin strands had a low method correlation, probably because the area available for viewing does not include the tail of the film. Data was also examined on films generated from XE2100 analyser flagging. Like flags were grouped together and compared with groupings of expected blood film findings. This data showed that groupings of XE2100 flags relating to toxic changes had a better correlation with CellaVision than microscopy. Other flag groupings relating to abnormal lymphocytes and platelets showed a better correlation with microscopy.

Conclusion: Normal films and white cell changes can be reported confidently using CellaVision without microscopic review. Abnormal RBC changes may require a microscopic review, at the operator's discretion. Microscopic review may be required to detect features which are often found only after scanning the whole blood film.

P4: KAVA CONSUMPTION AS A MAJOR CONFOUNDING FACTOR IN LIVER ABCESS
M. Sa Mainaulele Vu

Hepatic toxicity from manufactured herbal remedies that contain kava lactones has been reported in Europe, North America and Australia. There has not been any serious evidence for serious liver damage in kava using populations in the pacific islands who use aqueous kava extracts during weddings and large gatherings. There have been studies done in Fiji regarding an elevation in liver enzymes heavy kava consumers but nothing has been done on kava consumption as a confounding factor in liver abscess formation.

Aim: This research study presents some information showing an association between kava and liver abscess as well as other confounding factors.

Method: Data was collected over a 5 year period from 2006 to 2010 (September) for positive liver abscess patients from the Records department at the CWM hospital. Patients' history showed the independent variables of Kava, alcohol, smoking and diabetes. Data was collected from 193 folders and displayed diagrammatically in the result section of this study.

Results: Out of the 145 respondents, 123 (85%) participants had consumed kava and 22 (15%) did not consume kava but both had the outcome as liver abscess. People who drank kava and got the liver abscess are significantly higher than people who did not drink kava and had liver abscess. The most common organism isolated from the liver aspirate was Anaerobia. The age group of 30-40 years (Kava Drinkers) had the highest frequency of liver abscess. In conclusion; the data obtained during the course of this research suggests that people who had been exposed to kava drinking had a greater chance of getting liver abscess than those who were not exposed kava drinking. But a more in depth study needs to be carried out to calculate if kava is a confounding factor or not. Due to time constraints this study design was selected.

P5: MOLECULAR EPIDEMIOLOGY OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE FROM NORTH-INDIAN TERTIARY HOSPITAL
M. Shahid

Introduction: Albeit increasing reports of carbapenem-resistance genes from various countries, such reports are lacking from India. Therefore, this study was performed to look for the molecular epidemiology of bla genes responsible for carbapenem resistance in the Enterobacteriaceae isolates that were reported resistant to a carbapenem on primary antibiotic susceptibility testing.

Methods: The study was performed on routine samples subjected to culture and antibiotics susceptibility during September 2007 - April 2008. Bacterial cultures from 893 patients yielded growth of Gram-negative bacteria, and of which, sixteen isolates (E. coli 10; Klebsiella pneumoniae 6) were reported resistant to imipenem on primary antibiotic susceptibility testing. The minimum inhibitory concentration (MIC) for imipenem was determined as per the CLSI guidelines. These 16 isolates were further studied for the presence of carbapenem-resistance genes including blalMP, blalVIM, blalSIM, blalSIM, blalSPM, blalPER, blalKPC, and blalOXA by polymerase chain reactions (PCR). Since the isolates were also reported resistant to third-generation cephalosporins, these 16 isolates were also screened for the presence of blalCTX-M, blalampC, blalTEM, and blalSHV.

Results: Carbapenem-resistance was reported in 1.8% (16/893) isolates based on antibiotics susceptibility testing, however on detection of imipenem-MIC, only 0.8% (7/893) isolates were found as imipenem-resistant. Of these 16 isolates, carbapenem-resistance gene, blalVIM, was detected in only 3 (18.6%) isolates; all were K. pneumoniae. On cumulative analyses, any of the blal genes was detected in a total of 9.6% (15/16) isolates, blalCTX-M, blalampC, blalTEM and blalSHV were detected in 87.5% (14/16), 43.8% (7/16), 75% (12/16) and 31.3% (5/16) isolates, respectively. Maximum number (4/16; 25%) had a combination of blalCTX-M + blalTEM, followed by blalCTX-M, blalampC, blalTEM, and blalSHV in 3 (18.8%; 3/16) isolates.

Conclusion: Resistance to carbapenem is quite low in our area; only blalVIM was detected responsible for carbapenem resistance in our isolates. This is among the premier reports from India looking extensively for the molecular epidemiology in carbapenem resistant isolates.

P6: JC VIRUS: A CASE OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN AN ELDERLY WOMAN WITH RAPIDLY PROGRESSIVE NEURODEGENERATIVE DISEASE
J. Stirling

Introduction: Progressive multifocal leuкоencephalopathy (PML) is a rapidly progressive neurological disease that leads to death within a few months. PML is caused by reactivation of JC virus, a member of the polyoma group of viruses. Infection of oligodendroglial cells and astrocytes within the central nervous system leads to demyelination within the white matter. PML is typically seen in immunocompromised individuals. Case study: An 86-year-old woman (who showed no evidence of being immunocompromised) died 3 months after developing rapidly progressive neurological symptoms. A post-mortem examination of her brain was carried out to explore the clinical suspicion of Creutzfeldt-Jakob disease.
**P7: MUCOLIPIDOSIS II: PRENATAL DIAGNOSIS BY ELECTRON MICROSCOPY**

J. Stirling  
john.stirling@health.sa.gov.au

**Introduction:** Mucolipidosis II is an autosomal recessive disorder of oligosaccharide catabolism resulting in progressive psycho-motor retardation and skeletal abnormalities. Death occurs at age <5. The primary defect is a deficiency of N-acetyl-glucosamine-1-phosphate transferase activity that causes the mis-targeting of lysosomal enzymes with an accompanying build-up of un-degraded metabolites. Prenatal diagnosis is requested by affected families so that foetuses with mucolipidosis II may be terminated. The standard technique is to measure lysosomal enzyme activity in cultured chorionic villus cells or amniocytes; this takes 2-3 weeks. We investigated whether transmission electron microscopy (TEM) could detect mucolipidosis II-type lysosomes in chorionic villi within days.

**Methods:** Our investigation used prenatal chorionic villi samples from 20 individuals selected from 7 families with a known history of mucolipidosis II. All samples were tested as follows: (1) TEM of 2-4 villi fixed and processed using standard techniques and; (2) biochemical studies of cultured villus cells. Where available, positive cases were confirmed by TEM plus biochemical studies of cultured fibroblasts derived from autopsy tissue.

**Results:** Accumulations of un-degraded metabolites in lysosomes consistent with mucolipidosis II were found in 6 cases. Fourteen cases contained no abnormal lysosomes; these were diagnosed as negative for mucolipidosis II. Biochemical tests confirmed each of these diagnoses.

**Conclusions:** TEM identifies abnormal lysosomes in general. However, when this finding occurs in the context of a family history of mucolipidosis II, a specific diagnosis can be made with confidence. In affected families (where a pregnancy has a one-in-four risk of mucolipidosis II) TEM can therefore be used as a rapid screening technique that facilitates diagnosis.

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**P8: BABESIOSIS IN A RETURNED TRAVELLER – THE FIRST AUSTRALIAN CASE**

S. Tencic

- Babesiosis is a rare, severe and sometimes fatal tick-borne disease caused by various types of Babesia, a microscopic parasite that infects red blood cells. In New York state, the primary causative parasite is Babesia microti.
- The primary US animal reservoir is the white-footed mouse, Peromyscus leucopus. Additionally, white-tailed deer serve as transport hosts for the adult tick vector, I. scapularis. In Europe, the primary animal reservoir is cattle.
- The incubation period is 1–6 weeks.
- Illness is more severe with patients with no spleen and can prove fatal.
- We present a case of Babesiosis in an Australian woman who had travelled to Long Island (USA), Europe and Singapore between July – August 2010.
- She had been on a hayride and played golf on a farm in Southold – Eastern Long Island on 4th July (5 weeks earlier).

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**P9: EVALUATION OF A NEW AUTOMATED IMMUNOLOGICAL WHITE CELL DIFFERENTIAL**

M. Wheeler

**Introduction:** Our aim is to evaluate the Beckman Coulter HematoFlow™ system for automated immunological white cell differential analysis. This system incorporates a FP1000™ sample processor and a FC500™ flow cytometer and utilises Cytodiff™ which is a six antibody cocktail that provides a 9 part differential analysis of leukocytes and helps identify up to 16 cell subtypes. The results will be compared to the traditional automated cell counter and manual morphology results. We will also look at additional useful clinical information provided by this method.

**Methods:**
(a) Correlation: 400 samples will be analysed = 100 normals and 300 abnormalities (samples with blast flags, variant lymph flags, left shift flags, leucopenias, leucocytosis, lymphocytosis, monocytosis, and oncology patient samples). Automated differentials from the Beckman Coulter LH750 analyser, HematoFlow, and manual microscopy will be performed on all samples.
(b) Reproducibility: 3 samples will be run 10 times over a 24 hour period to assess reproducibility.

**Results:**
(a) Correlation (R2): data unavailable at time of abstract submission
(b) Reproducibility (CV): data unavailable at time of abstract submission

**Conclusions:** The HematoFlow allows for discrimination of white cells beyond traditional basic lineages (for example T or B lymphocytes), something impossible by morphology alone. It may be used to assist the morphologist with difficult or atypical cell identification, and as the system assesses of thousands of cells, this may lead to potentially better accuracy.

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**P10: SERUM ANTI-MÜLLERIAN HORMONE: REVIEW OF CLINICAL UTILITY**

M. Kolo, M. Lane, K. Tremellen

**Introduction:** AMH (Anti-Müllerian Hormone) belongs to the transforming growth factor β (TGF-β) superfamily. In females AMH is produced by the granulosa cells of the early developing antral follicles in the ovary. Females are born with approximately one million eggs and during their reproductive life egg numbers will decline as they are lost through natural attrition and ovulation. As the number of antral follicles decline, AMH levels fall indicating a diminished ovarian reserve.

**Aim:** To review and improve the clinical utility of AMH analysis and its clinical application.

**Method:** A retrospective analysis of previously published data had determined an AMH level of >14 pmol/L was required to be associated with a good ovarian reserve. Levels <14 pmol/L indicated the possibility of a diminished ovarian reserve and high levels, >30 pmol/L were associated with PCOS and a higher risk of OHSS during a stimulated cycle. Analysis of 840 women, aged 26–42 attending Repromed for fertility management resulted in the development of a new percentile graph which correlated the AMH value to the patient's peer age group. In addition oocyte retrieval data was compiled with relation to peer age groups thus enabling a correlation of both the AMH result and antral follicle count in determining ovarian reserve status (Egg Timer test).

**Results:** Patient results were reported with reference to the new age group parameters. For example, a female aged 27 with an AMH level of 15 pmol/L would have on the previous reporting method indicated a good ovarian reserve. However, when 15 pmol/L is plotted on the new graph it is now within the <25th percentile area, indicating that the patient has a low ovarian reserve when referenced to her stated age. AMH levels interestingly decline before an increase is noted in day 2–6 FSH analyses making it a more sensitive measurement of ovarian reserve.

**Conclusion:** AMH results when compared to peer age group related means can identify possible issues associated with the patient's fertility; currently not detectable by means of other hormone analysis. AMH is vital in predicting early ovarian reserve and when combined with transvaginal ultrasound (Egg Timer test) gives a more comprehensive understanding of the patient's overall ovarian reserve thereby giving the patient additional information regarding their fertility to make an informed decision.
Instructions to authors

The following instructions are based on the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals”, also known as the Declaration of Vancouver, and on the Australian Government Style manual: for authors, editors and printers, 6th edition, 2002. URLs were correct on September 29th, 2008.

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The Australian Journal of Medical Science (AJMS) will consider for publication any paper relevant to the field of Medical Science. Disciplines include blood banking, clinical biochemistry, haematology, histopathology, immunology, microbiology and molecular biology. Areas of general interest to medical laboratory scientists, including toxicology, epidemiology, public and community health, and professional and management issues will also be considered.

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All individuals listed as authors must have made a substantial contribution to the conception and design of the study, the acquisition of data or the analysis and interpretation of data; the drafting of the article or revising it critically for important intellectual content; and final approval of the version to be published. The corresponding author must take responsibility for obtaining permission from all the authors for the submission of any version of the manuscript and for any changes in authorship.

When the manuscript is submitted the authors must disclose any potential conflict of interest and/or commercial support.

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Number pages consecutively commencing with the title page.

Arrange the article in the following sequence:

- Title page
- Abstract and key words
- Main Text
- Acknowledgements
- References
- Tables - each table, complete with title and footnotes, on a separate page
- Legends for illustrations.

Authors should ensure that their manuscript communicates their ideas and concepts simply and clearly so that the article is easily read and understood. Authors are strongly recommended to refer to the recommendations on reporting standards as outlined in the statements and checklists of the CONSORT group (see: http://www.consort-statement.org/) and similar groups such as STARD (see: http://www.stard-statement.org/). The principles outlined in these standards may be used as general guidelines and not just as applied to clinical trials and diagnostic studies.

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The title of the article should not exceed three lines (40 characters per line), including punctuation and spacing. All authors must be identified on the title page (e.g., William Smith, Susan Yeo, ...”). Where applicable, the title page should also include the name
of the institution with which each author is affiliated and to which the work should be attributed. In the case of multiple authors, the name, postal address, email address, telephone and facsimile number of the author responsible for correspondence relating to the manuscript should be indicated.

Abstract and Keywords

The abstract should be approximately 150 words and should make sense when read alone or in conjunction with the article. The abstract should be a concise overview that describes the important details of the article including the purpose of the study/investigation, basic procedures (study subjects/experimental animals/observational and analytic methods) and the results and principal conclusions. New and important aspects of the work and its implications may also be included. References should not be included.

Three to ten keywords may be listed. Authors are advised to comply with the terms from the Medical Subject Headings (MeSH) list from Index Medicus (see http://www.nlm.nih.gov/mesh/). Keywords should be given below the Abstract.

Text

The style of writing should conform to acceptable English usage. Do not use slang, medical jargon or unnecessary abbreviations. Accepted spelling is the first choice given in the latest edition of the Macquarie Dictionary.

Wherever possible observational or experimental articles should be divided into sections headed:

- Introduction
- Materials and methods
- Results
- Discussion
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For other types of articles such as commentaries, reports and reviews, use an appropriate format or consult the Editors for guidance.

Introduction

Clearly state the purpose of the article leading the reader from the known to the unknown. Summarise the rationale for the study and state the question to be answered as appropriate. Give only strictly pertinent references, and do not review the subject extensively.

Materials and methods

Present the materials and methods in a logical sequence. Describe the selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Notification of ethics approval must be given where relevant. Identify the methods, apparatus and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Adequately describe new or substantially modified methods. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not identify patients or hospitals without consent.

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Present the results in the same sequence as given in the Materials and methods; use tables and illustrations where these will help the reader understand the work being presented. Do not repeat in the text all the data in the tables or illustrations.

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Indicate the new and important aspects of the study and emphasise the conclusions that follow. Do not repeat in detail data given in the Results section and do not add new data. Include in the Discussion the implications of the findings and their limitations and compare the observations to other relevant studies. Recommendations may be included if appropriate. Link the conclusions with the goals of the study and answer the experimental question stated in the Introduction. However, avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.

Acknowledgements

Acknowledge individuals who have made substantial contributions to the study including technical work and financial support. Authors are responsible for obtaining consent from all the individuals acknowledged by name as inclusion may be interpreted as an endorsement of the article’s contents.
References

The AJMS uses a modified Harvard System (author-date system).

Throughout the body of the manuscript cite the author/s name and the publication year in parentheses as in the following examples:

(i) Research in this area (Jones 1999) …

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ii) Personal Author(s) of a book:

iii) Editor, Compiler, Chairman as Author:

iv) Chapter in Book:

v) Online documents:

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Number tables consecutively with Arabic numerals and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in headings. Explain in footnotes all non-standard abbreviations used in each table.

For footnotes, use the following symbols in this sequence:

* † ‡ § ¶ ** ††

In preparing tables, consideration should be given to the page width of the Australian Journal of Medical Science. All tables should be prepared for publication vertically. In the text, cite each table in consecutive order, and mark in the margin of the text its approximate location.

If data from another published or unpublished source is used, written permission must be obtained and a copy must accompany the manuscript.

Illustrations

Colour illustrations may be submitted on a CD. Images should be scanned at a minimum of 300 dpi.
When plotting points, the following symbols are preferred:

- ○ ▲ ▼ □ ■

In most instances, figures will be reduced to one column in width. All letters and numbers should be drawn to be at least 1.5 mm high after reduction, symbols at least 1.0 mm. Titles for illustrations belong in the legends for illustrations and not on the illustrations themselves.

Photomicrographs must have internal scale markers and the magnification must be stated. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.

Cite each figure in the text in consecutive order, e.g., “Figure 1 illustrates …” or “… as shown (fig. 2)”. If a figure has been published, acknowledge the original source and submit with the manuscript written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

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When symbols, arrows, numbers, or letters are used to identify parts of illustrations, identify and explain each one in the legends. The figure legend must contain a boldface (a) name (“Figure” + arabic figure number) and (b) substantive title.

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Use only standard abbreviations (see list of commonly used abbreviations, below).

Avoid abbreviations in the title. The full term for which an abbreviation stands must precede its first use in the text unless it is a standard abbreviation for a unit of measurement.

Report measurements in the units in which the measurements were made. In most countries the International System of Units (SI) is standard.

### Commonly used abbreviations

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The following are useful sources of information. The first two publications are used by the AJMS as standard references.

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