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Flow cytometry testing for PNH cells at a single referral laboratory during 2009

Ross D Brown, Karieshma Kabani, Esther Aklilu, Shihong Yang, Douglas Joshua
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Abstract

The definitive diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) requires testing by multiparameter flow cytometry to detect and quantitate the size of both the red blood cell (RBC) and white blood cell PNH clones. These clones have a reduced expression of specific proteins binding to the glycosyl-phosphatidyl-inositol (GPI) anchor. Testing and reporting of PNH has evolved in recent years with new markers replacing the more traditional markers (e.g. FLAER, CD24, CD66b replacing CD16, CD59 on granulocytes). The introduction of assays with a high sensitivity and specificity is essential to comply with both the regulatory requirements for the prescription of the new drug, Eculizimab, and the new testing guidelines issued by the Australasian Flow Cytometry Group. We now review the results from 15 patients with PNH tested in our laboratory during 2009 and highlight important changes we have made to methodology.

Key words: Paroxysmal nocturnal hemoglobinuria, CD59, FLAER, flow cytometry.

Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare disorder caused by an acquired genetic mutation of the PIG-A gene resulting in a missing glycosyl-phosphatidyl-inositol (GPI) anchor which normally binds to a range of membrane proteins including a complement inhibitor, which when reduced or absent makes the cells vulnerable to complement attack (Miyata et al 1993; Miyata et al 1994; Parker et al 2005). The true incidence of the condition is not known. Extrapolation from demographic studies in the United Kingdom (Hill et al 2006) suggests that there should be about 350 patients in Australia however a recent survey indicated that there are currently only 69 patients known to haematologists (Kwasha, unpublished observation). The disease is characterised by intravascular haemolysis and episodes of haemoglobinuria which are more obvious at night and early morning (Parker et al 2005; Hillmen et al 1995). The defect has been studied extensively and it is now known to be derived from a clone of stem cells present in red blood cell (RBC), white blood cell (WBC) and platelet lineages. The unusual sensitivity to normal complement C3 in plasma, leads to an ongoing intravascular haemolysis of RBC and often a diminished bone marrow production of WBC and platelets. Patients become transfusion dependent and iron deficient but it is arterial and venous thrombi that are the major cause of death (Parker et al 2005; Hillmen et al 1995). Venous or arterial thromboses account for approximately 40% to 67% of PNH-related deaths (Hillmen et al 1995; Moyo et al 2004; Hillmen et al 2007; Socié et al 1996) while renal failure has been identified as the cause of death in approximately 8% to 18% of PNH patients (Socié et al 1996).

Although allogeneic transplantation of haemopoietic stem cells is the only known curative therapy, treatment for this condition is more likely to be symptomatic with periodic blood transfusions (Hillmen et al 1995; Parker et al 2005). A new therapy, involving a monoclonal antibody to complement C5 (Eculizimab), has recently been released and has significantly reduced transfusion requirements, the incidence of thromboembolism and disease-related symptoms, leading to a higher quality of life (Hillmen et al 2006). However, Eculizimab is a very expensive drug and although it is anticipated that it will soon be made available to patients in Australia under the Life Saving Drug Program (LSDP), this will only be after extensive clinical and laboratory evidence is provided for each patient. Thus laboratories need to be aware of the prescribing guidelines when issuing patient results.

Small numbers of PNH cells are also commonly found in patients with aplastic anaemia (68% of patients) and myelodysplasia (42% of patients) (Sugimori et al 2006; Ishikawa 2007) when a high sensitivity assay is applied. The presence of even minor PNH clones (>0.003%) in these patients has been associated with a better prognosis...
following immunosuppressive therapy (Sugimori et al 2006; Ichikawa et al 2007). Currently, the detection of these minor clones is rarely performed in Australian laboratories and if required would present some technical challenges to the sensitivity levels of the procedures used in many existing flow cytometry laboratories.

The diagnosis of PNH was for many years based on the Ham’s test, first introduced in 1939, which showed that PNH RBC are lysed in acidified serum by factors including complement (Ham et al 1939). Other tests, like the sugar water test and sucrose haemolysis assay, were later used by many laboratories (Hartmann et al 1966; Hartmann et al 1970). In the mid-1990s these assays were gradually replaced by flow cytometry and today only multiparameter flow cytometry should be used for the definitive diagnosis of PNH. Flow cytometry detects the loss or absence of proteins which are normally bound to the GPI anchor. There has been an evolution of the testing procedure largely owing to the availability of new reagents, in particular some new monoclonal antibodies (CD24, CD66b), fluorochromes and a fluorochrome-conjugated (Alexa 488) version of a non-lysing, mutated form of proaerolysin (FLAER) which allows an improved high sensitivity multiparameter flow cytometry. It is important to test RBC as well as granulocytes and/or monocytes and also report the clone size (Hall et al 1996; Richards 2007). The size of the RBC clone is likely to be reduced owing to haemolysis and recent blood transfusion of normal cells.

In 2009 the Australasian Flow Cytometry Group (AFCG) issued guidelines for best practice multiparameter flow cytometry to detect and report the presence of PNH cells (AFCG 2010). There is some flexibility in the choice of GPI anchor proteins which can be used under these guidelines but the principles of first performing gating strategies for optimal lineage identification and then using the most appropriate reagents to demonstrate the loss of expression are now defined and agree with international best practice (Richards et al 2007). The AFCG guidelines were designed to produce some uniformity in testing and reporting in Australia and thus enhance the ability to obtain Ecuzimab therapy for patients when necessary. In this article we review the testing of samples from 15 patients with PNH which were tested in our laboratory during 2009. As we receive referred samples from a number of centres, this is one of the largest cohorts of patients with PNH studied in Australia during this period and our recent experience may be of interest to laboratories that rarely have a true PNH patient and to laboratories that are reviewing their current testing and reporting practice.

**Materials and methods**

EDTA blood samples were used. Clinical details of patients are not available as many samples were from patients at other centres. For RBC analysis, 5 μL aliquots of whole blood were first washed with 2 mL phosphate buffered saline pH 7.3 (PBS) and then 10 μL of anti-CD59 FITC was added (AbD Serotec, Oxford, UK) for 15 min. Cells were washed with PBS and resuspended to 2 mL. For white blood cell analysis, the sample was centrifuged at 400g for 10 min, buffy coat was removed, washed twice with PBS and resuspended in 1 mL of PBS. Aliquots of 100 μL washed buffy coat were added into a minimum of 2 tubes for white blood cell analysis and then 2 mL of lyse reagent was added to each tube. After 10 min incubation, tubes were centrifuged and washed with 2 mL PBS; 10 μL of anti-CD14 PE (DAKO, Glostrup, Denmark) was added to one tube and 20 μL of anti-CD24 PE (BD Biosciences) was added to the other tube while 10 μL of FLAER (Cedarlane, Burlington, Canada) and 10 μL of anti-CD33 APC (BD Biosciences) was added to each tube. Tubes were left in dark for 15 min, washed and resuspended in about 0.5 ml PBS. RBC and white blood cells were analysed using different protocols on either a BD ARIA II (BD Biosciences) or a Beckman Coulter EPICS flow cytometer. A minimum of 50,000 total events were counted and for samples with small numbers of PNH cells a minimum of 100 PNH cells were counted. Granulocytes and monocytes were first gated on CD33/SS and then a scattergram was produced for CD24/FLAER and CD14/FLAER. Isotype controls were omitted as they do not assist the analysis. Normal cells (not PNH) were tested with each assay batch. The addition of 10 μL of Table 1 CD45 PerCP-Cy5.5 (BD Biosciences) was used when required to differentiate between primitive myeloid cells and PNH cells.

**Results**

Our laboratory has developed a systematic approach to the detection and quantitation of the PNH clone in RBC, granulocyte and monocyte populations. The approach closely follows the recently released AFCG guidelines (AFCG 2010).

RBC were analysed in a separate tube. The main RBC population was gated on forward scatter vs side scatter (FS/SS) and histograms of CD59 expression were produced to quantitate RBC which were CD59 absent (Type III) and also RBC which were CD59 deficient (Type II). Fig. 1A illustrates the expression of CD59 on normal RBC and Fig. 1B illustrates the expression of CD59 on a patient we studied in 2006 who has a classic mixture of normal (Type I), deficient (Type II) and absent (Type III) CD59 expression.
The heterogeneity of CD59 expression on the RBC of the 15 patients with PNH studied in 2009 is shown in Fig. 2 and Table 1. The results in Fig. 2 suggest that the classic “text-book” image of three clear RBC populations as shown in Fig. 1 is not common. It is worth noting that most patients with a subpopulation of RBC with normal CD59 expression were already transfusion dependent, though precise details are not available as many samples had been referred.

**Table 1**

Percentage of RBC, neutrophils and monocytes that are part of the PNH clone.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>% of RBC in PNH Clone</th>
<th>% Type III RBC</th>
<th>% Type II RBC</th>
<th>% Neutrophils in PNH Clone</th>
<th>% Monocytes in PNH Clone</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>84</td>
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<td>6</td>
<td>0</td>
<td>93</td>
<td>99</td>
</tr>
</tbody>
</table>

NT= Not tested

**Figure 1**

Flow cytometric histograms of CD59 expression on (A) normal red blood cells and (B) red blood cells from a patient with PNH showing a mixture of Type I (normal), Type II (reduced) and Type III (absent) CD59 expression.

**Figure 2**

CD59 expression on red blood cells of all 15 patients tested during 2009 demonstrating the variable CD59 expression profiles.
For the analysis of granulocytes and/or monocytes, the first step was to perform a lineage gate from a CD33/SS scattergram (Fig. 3A). Granulocytes were then analysed for CD24/FLAER and monocytes were analysed for CD14/FLAER expression in scattergrams (Figs 3B, 3C). PNH cells and normal cells are clearly separated. In rare cases when it was necessary to validate that the cells with low CD24 and FLAER expression were PNH clonal cells and not immature myeloid cells, anti-CD45 PerCP-Cy5.5 was added and the cells with reduced CD24 expression were analysed on a CD45/SS scattergram. True PNH cells display a high CD45 expression whereas immature myeloid cells and myeloblasts may have decreased CD24 expression but will also have a reduced CD45 expression. In reality this will not be an issue if a satisfactory lineage gate for CD33/SS is applied.

Discussion

During 2009, we tested blood samples from 15 different patients with PNH. The size of the RBC PNH clone (total RBC, Type III cells and Type II cells), granulocyte and monocyte clones are indicated in Table 1. While Fig. 1 illustrates a classic three peak histogram of CD59 expression on Type I, II and III RBC, in reality the CD59 expression profile histograms are not always so well-defined. Histograms of CD59 expression on RBC from each patient are shown in Fig. 2 to demonstrate the variability of expression on RBC. Patients 4, 5, 6, 7, 8, 9 all had both a clone of cells with reduced CD59 expression (Type II cells) and a clone of cells with no CD59 expression (Type III cells). When the size of the RBC PNH clone was significantly less than the granulocyte and/or monocyte clone, the patients had recently received a blood transfusion of normal RBC. Fig. 3 illustrates the detection of the granulocyte PNH clone by CD24 and FLAER. When a three laser flow cytometer is used, a careful selection of fluorochromes will allow a single tube assay for both granulocytes and monocytes, including lineage gating with CD33/SS (or CD15/SS) and PNH cell validation (CD45/SS) if required.

The recent availability of both an effective therapy for patients with PNH and also new testing reagents has resulted in many laboratories reviewing the testing requirements and the most appropriate procedures for a precise diagnosis of this condition. We therefore considered it appropriate to review and report on the performance of our testing during 2009 and to highlight important features of the AFCG guidelines that were introduced in 2009 for flow testing of PNH (AFCG 2010). As a quantitative determination of the size of the PNH clone in both the RBC and granulocyte populations is a requirement for the release of the new drug to patients in Australia, it is important that laboratories that test for PNH review their methodology and reporting practices in the context of the new AFCG guidelines.

The changes made in our laboratory include the laboratory reports which now clearly state the percentage of both RBC and granulocytes that are PNH cells. FLAER has replaced CD59 as the preferred marker on granulocytes and monocytes. Gating strategies for white blood cells now begin with a lineage gate, preferably using either CD33/SS but CD15/SS is also satisfactory. CD45/SS can then be used as a post-analysis step to confirm that the proposed cell population are PNH cells although this may prove to be necessary only in patients with myelodysplasia and aplastic anaemia as these patients may have a small number of PNH clones (Sugimori et al 2006; Ishikawa et al 2007). The identification of minor PNH clones in these patients is a good prognostic factor and the current challenge for flow cytometry laboratories that test for PNH cells is to achieve the very low levels of sensitivity (0.003%) which have been claimed to be essential for the discrimination between the good and poor prognostic patients (Sugimori et al 2006). Although further studies need to be performed to validate that this sensitivity level is clinically important, methodologies...
that follow the new AFCG guidelines should be able to achieve this sensitivity if required by counting additional cells. Our laboratory currently does not attempt to achieve a sensitivity level below 0.01%.

There are a few additional technical considerations that need to be considered (AFCG 2010). Isotype controls do little to assist the gating for any cell lineage when testing for PNH as it is more important to assay the positive expression in normal cells. Unlike most other flow cytometry assays, the PNH assay needs to determine the presence of cells with reduced and/or absent expression, not positive expression. Single colour flow cytometry using anti-CD59 is satisfactory for analysis of RBC in most samples, however gating using anti-CD235 can assist with accurately identifying RBC lineage in the presence of other cell debris when the detection of minor RBC populations is required. The use of the fluorochrome phycocerythrin (PE) rather than fluorescein isothyocyanate (FITC) could be used to increase the sensitivity of anti-CD59. Some clones of anti-CD59 are thought to be better than others. The MEM43 clone is recommended (AFCG 2010). The use of anti-CD16 on granulocytes can cause problems with interpretation, due to the polymorphism of this molecule. Patients with classic PNH normally have a large proportion of cells with reduced CD59 expression. However a clear quantitation of each of the expression peaks, as illustrated in Fig. 1, is not always possible as shown in Fig. 2. Analysis of lymphocytes is not recommended and bone marrow samples are not suitable for analysis. Blood samples can be analysed up to three days after collection however it is important to realise that Type III RBC may lyse during storage and processing.

References


The changing regulatory environment of in vitro diagnostics: implications for sponsors, manufacturers and laboratory users

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Abstract

Currently most in vitro diagnostic devices (IVDs, clinical pathology tests) are exempt from any form of pre-market assessment by the Australian Government Department of Health and Ageing Therapeutic Goods Administration (TGA). The TGA believes that current regulation is not in line with international best practice nor is it ensuring that public or personal health are appropriately protected by the current regulation applied to the introduction of a rapidly developing array of new tests. The TGA has therefore proposed a revised regulatory framework that will now see all IVDs undergo pre-market regulatory assessment in accordance with their level of risk. The new framework provides for four classes of IVDs ranging from Class 1 (lowest risk) to Class 4 (highest risk) and includes for the first time in-house manufactured laboratory tests. At the time of publication of this manuscript, it was anticipated that these changes would take effect from 1 July 2010 with a transition until 30 June 2014.

The purpose, scope and details of how the revised framework will function and effect laboratory scientists and sponsors/manufacturers are the subject of this review.

Keywords: Laboratory personnel, staff development, in-service training, medical science, scientist, pathology, professional status.

The author acknowledges that the information included in this review is current at the time of writing but is subject to change by the TGA prior to and during the implementation of the revised regulations. Any opinions expressed in this review are those of the author who is a regulatory consultant, and not necessarily those of Brandwood Biomedical or DevDx Clinical.

Introduction

Most diagnostic pathology tests are currently exempt from any form of pre-market regulatory scrutiny and are only subject to post market monitoring and vigilance by both the supplier and the Australian Government Department of Health and Ageing Therapeutic Goods Administration (TGA). In order to align with what the TGA believes is international best practice and ensure that public and personal health are adequately protected, the TGA has proposed a revised framework for the regulation of in vitro diagnostic devices (IVDs). Essentially, the new framework will see IVDs regulated as a subset of medical devices. This will require prior to its implementation, an amendment of the Therapeutic Goods Regulations (Therapeutic Goods Amendment (Medical Devices) Act 2002; Therapeutic Goods Act 1989). The new regulations will see all IVDs classified and regulated according to risk categories ranging from Class 1 (lowest risk) to Class 4 (highest risk). Unlike the existing regulations, all in-house manufactured IVDs will now also be included under this umbrella. Existing IVDs, irrespective of their class, will need to transition to the new framework within four years of the introduction of the regulations (TGA 2009).

The TGA operates as a full cost recovery agency deriving its income from fees collected from sponsors and manufacturers in assessing safety, quality and efficacy claims for their products prior to inclusion on the Australian Register of Therapeutic Goods (ARTG). A major consequence of the new regulations will therefore be a substantial increase in regulatory processing costs for the Australian sponsor or manufacturer: 1) by virtue of the need to have all IVDs assessed and included on the ARTG; and 2) as a result of the TGA’s policy to review its fees and charges annually.

What is an IVD?

As specified on the TGA website (2009) IVDs are, “in general, pathology tests and their related instrumentation used to carry out testing on human samples.” Importantly,
results from these tests must be intended to assist clinical diagnoses or make clinical management decisions. IVDs therefore include tests used in laboratories, at the point of care (e.g. in the Intensive Care Unit) and in the home (self testing). Under the proposed new Australian regulatory framework and as described on the TGA website (2009), IVDs will be specifically defined thus

- it is a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with another diagnostic product for in vitro use; and,
- it is intended by the manufacturer to be used in vitro for the examination of specimens derived from the human body, solely or principally for:
  - giving information about a physiological or pathological state or a congenital abnormality, or
  - determining safety and compatibility with a potential recipient; or
  - monitoring therapeutic measures.

The following tests are excluded from the scope of this definition:

- products intended for general laboratory use that are not manufactured, sold or presented for use as an IVD.
- products that are not intended to have a therapeutic indication such as tests for parentage; tests for alcohol and illicit drugs (including sports screening).

How are IVDs currently regulated in Australia?

Currently, in accordance with the Therapeutic Goods Regulation 1990, most IVDs are exempt from any form of TGA pre-market assessment, although manufacturers and sponsors are required to comply with post-market regulations and the Therapeutic Goods Advertising Code 2007. “Sponsors” are defined as a person or company who is legally responsible for the supply of a product in, or exported from Australia. Manufacturers may also be the sponsor but take responsibility for the design and development and manufacture of their products. In Australia there are few manufacturers so most IVDs supplied in Australia are manufactured overseas and sold and distributed by Australian sponsors.

IVDs for supply in Australia are classified according to Table 1 and are either registered or listed in the Australian Register of Therapeutic Goods (ARTG) or exempt from entry in the ARTG.

Listed IVDs are routinely subjected to an administrative review by the TGA that includes evidence of Good Manufacturing Practice (GMP), instructions for use, details of any human or animal origin material, labeling and promotional material. Registrable IVDs, however, undergo an extensive pre-market review of the product’s Technical File including full safety and performance evaluation by the TGA’s sub-contracted reference laboratory in Victoria (NSRL).

Australian manufacturers must obtain a GMP licence issued by the TGA; whereas overseas manufacturers require an ISO 13485 certificate (for their quality management system) or a Conformité Européene (CE) certificate issued by a Notified Body designated in Europe for the purposes of the In Vitro Diagnostic Medical Devices Directive (98/79/EC).

Since most IVDs used in the Australian market fall within the exempt category, sponsors and manufacturers, largely, have not been exposed to the latter regulatory burden or cost associated with the TGA pre-market assessment process, thus enabling a wide range of tests and instrumentation to be made available. Under the proposed Australian regulatory framework this will change.

<table>
<thead>
<tr>
<th>ARTG status</th>
<th>IVD “Type”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registrable</td>
<td>Goods for diagnosis and monitoring of HIV, HCV</td>
</tr>
<tr>
<td>Listable</td>
<td>Diagnostic goods for in vitro use that are:</td>
</tr>
<tr>
<td></td>
<td>- For home use</td>
</tr>
<tr>
<td></td>
<td>- That incorporate material of human origin</td>
</tr>
<tr>
<td></td>
<td>- That are sampling containers</td>
</tr>
<tr>
<td></td>
<td>- Products on the Pharmaceutical Benefits Schedule</td>
</tr>
<tr>
<td>Exempt</td>
<td>All other IVDs</td>
</tr>
</tbody>
</table>

Why has the TGA proposed regulatory changes?

Like medicines, medical devices and IVDs are regulated to ensure that they are used as intended and do not harm patients or users. Like most regulatory agencies worldwide the TGA believes that the degree of regulatory pre-market assessment and post-market control should be commensurate with the degree of risk in using that particular device. The TGA has assessed their current model and in order to better align it with what they consider regulatory best practice and adhere to these principles, they feel that the current model is inadequate (TGA 2009). Certainly, only HIV and HCV tests are currently rigorously assessed for safety and performance.
therefore most available tests on the market have not undergone any form of pre-market regulatory scrutiny at all. The TGA has therefore proposed that in order to provide a better level of protection of personal or public health, all IVDs should undergo a similar level of regulatory assessment and control. However, it is important to remember that Australian clinical laboratories are subject to strict laboratory accreditation requirements as set by the National Pathology Accreditation Advisory Council (NPAC) and monitored by the National Association of Testing Authorities (NATA); this greatly minimises this inadequacy.

Since the speed, cost and regulatory control exerted over medical technology development continues to increase, according to the TGA, there is a real need for regulatory authorities to introduce a framework that not only consistently ensures public and personal protection, but allows manufacturers and sponsors to expeditiously bring new products to the market by applying uniformity of regulation across international jurisdictions.

Increasingly IVDs are also being developed for point of care testing and for home use and many of these are for serious diseases. Again, the TGA believes that current regulation does not provide assurance of public protection in this environment.

Finally, as indicated above, the current model is not aligned with international best practice that takes into consideration quality, safety and risk management practices and provides the degree of flexibility and capacity that is required to keep abreast of new testing platforms and technologies and emerging diseases.

The proposed new Australian IVD regulations are based on the GHTF (Global Harmonisation Task Force)

Under the auspices of the National Coordinating Committee on Therapeutic Goods (NCCTG), the TGA in close consultation with the IVD Industry in Australia has proposed a revised regulatory framework for all IVD products supplied in Australia. As for the medical devices framework, the upcoming IVD system is based largely on the Canadian classification system, some elements from the European system (Directive 98/79/EC) with the inclusion of certain Global Harmonisation Task Force (GHTF) recommendations (GHTF 2008; TGA 2009).

The new framework is modeled on the GHTF (2008) recommendations which are centred on a four-level public and personal risk-based classification scheme which is intended to overcome the shortcomings of the current Australian and European schemes.

Essentially the new framework will see IVDs regulated as a subset of medical devices. This will require, prior to its implementation, an amendment of the Therapeutic Goods Regulations (Medical Devices) 2002. There will be no need to change the Therapeutic Goods Act itself.

The new regulatory framework as proposed will have the following major features (GHTF 2008; TGA 2009):

- all IVDs falling within the scope of the definition (for therapeutic use) will be included.
- legal supply will be contingent on inclusion of all IVDs onto the ARTG.
- all IVDs to comply with a set of Essential Principles (including those generic to all medical devices and a new set specific to IVDs) for quality, safety and performance of the IVD throughout the product life cycle
- two major elements intended to demonstrate objective evidence of safety and performance, benefits and risks:
  - pre-market: conformity assessment.
  - post-market: vigilance/surveillance, adverse event reporting and recalls.
- a four-tiered classification scheme based on different levels of risk for each class of device that determines the level of conformity assessment.
- the class is determined through a set of rules that determine risk, rather than being prescriptive (as it is the case with the European regulatory system).

Unlike the current regulatory environment, the new framework will see all commercial IVDs for therapeutic use included on the ARTG prior to being imported, supplied or exported from Australia. Provisions (under the current Special Access or Clinical Trial Notification Schemes) for access to unapproved IVDs, such as for use during clinical trials will remain.

Importantly, a major change in this framework is the intended regulation of “in-house” manufactured IVDs. In-house IVDs are developed and used within a laboratory or laboratory network and are widely used for clinical diagnosis and management.

The TGA (2007) regards as a laboratory network an organisation whose activities span more than one field of testing or program, or which operate at multiple sites within a field, or involve a combination of multiple sites and fields/programs under a single Approved Pathology Authority, with a single quality management system.

The proposed method for regulating in-house IVDs is discussed below.
The goal of GHTF is to provide a collaborative forum for representatives of member nations’ regulatory authorities and industry representatives from the European Union, the United States of America, Japan, Canada and Australia to promote international convergence in regulatory requirements and practices; thereby presumably streamlining the regulatory process and promoting earlier access to medical devices.

On the surface, it appears reasonable that the TGA has sought guidance from the GHTF in the development of their new regulatory framework. However, to date, no other country has actually adopted the GHTF recommendations, so if the new regulations go ahead as planned, Australia will have a regulatory system for IVDs that is in fact unique. Some corners of the industry feel that the TGA may be pushing ahead too early.

The TGA has now targeted this implementation during 2010, although there is good reason to believe that this may not occur. The new IVD regulatory framework was originally intended to be implemented as part of the failed Australian and New Zealand combined regulatory agency project, the Australia New Zealand Therapeutic Products Authority (ANZTPA), since around 2002. There have been many delays to this project and likewise for the introduction of the IVD framework, partly as a result of the TGA experiencing difficulty with establishing a mechanism for dealing with the large bulk of IVDs used in Australia that are imported.

It will be interesting to observe when and how the implementation proceeds.

Once implemented, however, the TGA will provide for a four-year transition period that will assist sponsors and manufacturers develop and prepare the necessary regulatory technical documentation required.

**Classification rules**

IVDs will be classified in accordance with the level of risk posed to either the individual or public which arises directly through the use of the individual IVD (GHTF 2008; TGA 2009).

There are four risk classes:

- **Class 4 IVD** – high public health risk.
- **Class 3 IVD** – high personal risk or moderate public health risk.
- **Class 2 IVD** – low public health risk or moderate personal risk.
- **Class 1 IVD** – no public health risk or low personal risk.

The manufacturer is responsible for determining the classification of each of their products by applying the above classification rules. In doing so, they must consider the intended use of the IVD and the significance of the final result to diagnosis or clinical management.

If more than one classification rule applies, the IVD will assume the highest classification level.

The lowest risk class, Class 1, includes items with low private and public risk, such as reagents, specimen containers and microbiological culture media – as well as IVDs intended for export only.

Class 2 IVDs include tests such as pregnancy tests and other tests that are not the sole determinant for diagnosis of a disease.

Class 3 IVDs include any tests for infectious diseases, tests that could put an individual in danger if it gives an erroneous reading is given and tests that represent the sole determinant for a diagnosis.

Class 4 includes high risk tests, including those that screen for transmissible agents in blood, such as HIV and hepatitis tests.

Further examples of IVDs falling within each classification can be found at: [http://www.tga.gov.au/ivd/overview.htm](http://www.tga.gov.au/ivd/overview.htm)

**Essential Principles**

The Essential Principles (EPs) set out the requirements relating to the safety and performance characteristics of the IVD that the manufacturer must be able to demonstrate through the application of appropriate standards and verification and validation processes.

Before registration of an IVD the manufacturer must satisfy themselves and the regulator that their product works as intended, that all hazards and risks to the patient or user have been addressed and that on balance the benefits derived from use of the IVD outweigh any risks.

The regulator does not mandate which EPs apply, it is up to the manufacturer to determine how to demonstrate their product’s performance and safety by selecting the appropriate EPs, then showing how they comply with each selected EP.

The EPs are divided into two main types:

- general principles – which apply to all medical devices, and
- specific principles – which are only applicable to some medical devices and include new principles specific to IVDs, for example: the IVD must be designed and manufactured in a fashion that ensures analytical and clinical characteristics will meet its intended use and addresses accuracy, precision, sensitivity, specificity, stability, control of known interference and

**Conformity assessment**

Having established how to comply with the relevant EPs, under the revised IVD framework, manufacturers will also need to demonstrate conformity with Australian regulatory requirements in order to place their product on the ARTG. The term ‘conformity assessment’ defines those activities that a manufacturer must undertake to demonstrate conformity with applicable regulatory requirements. For Australian manufacturers, the degree of regulatory burden, time and cost, especially for inclusion of their higher risk products is substantial. As with EPs, the manufacturer is responsible for choosing the conformity assessment procedure that is appropriate to their IVD’s intended use and risk classification.

Procedures for demonstrating conformity include:

- manufacturer self-assessment (as for lowest risk IVDs).
- declaration of conformity (holding technical information but not submitting it for review).
- full regulatory review and certification of the quality management system (QMS) and product design by the TGA (as for Class 4 IVDs).
- in order to supply IVDs, a conformity assessment certificate will be required to be issued by the TGA for:
  - Australian manufacturers of Class 2 or Class 3 IVDs.
  - all Class 4 IVDs (for Australian AND overseas manufacturers).

In some circumstances a conformity assessment certificate issued by a notified body overseas may be accepted in lieu of the need for a TGA certificate.

**What are manufacturer and sponsors requirements under the new regulatory framework?**

The classification of the IVD will determine the minimum conformity assessment procedure(s) that the manufacturer must apply to demonstrate compliance with the EPs. The degree of regulatory compliance and scrutiny by the TGA increases with the degree of risk and therefore the higher the classification of the device. The degree of technical (quality and performance) evidence required to be held and submitted by the manufacturer and sponsor to the TGA for review, likewise increases, progressively from Class 1 through to Class 4. Regulatory requirements may include:

- operation of a quality management system such as ISO 13485.
- documentation of clinical evidence to support the IVD’s intended use.
- product testing using in-house or independent vendors.
- the need for and frequency of independent external audit of the manufacturer’s QMS.
- independent external review of the manufacturer’s technical data.

The regulatory burden on the manufacturer and sponsor, will, therefore, under the new regulatory framework, be much greater than exists currently. The potential consequences of such an increase in regulatory burden are discussed below.

**How could commercial IVDs be affected by the new framework?**

For IVDs sold commercially in Australia, the conformity assessment procedures will generally incorporate those aspects already applied to medical devices, including certification of a QMS, surveillance audits and post-market vigilance. Based on the classification of the IVD the manufacturer will select an appropriate conformity assessment route from the In Vitro Diagnostic Medical Devices Directive (98/79/EC). The manufacturer will also need to make an Australian Declaration of Conformity (DOC) consistent with TGA requirements. The extent of technical documentation needed to be held by the sponsor and manufacturer for compliance to the Essential Principles (EPs) and Quality Management Systems (QMS) clearly increases in line with the risk and classification of the IVD. Documentation may range from self-declaration of conformity to the EPs and existence of a QMS (without TGA assessment) for certain Class I IVDs to the requirement for a fully compliant ISO 13485 (TGA certified) QMS, an assessment of the IVD’s design dossier and for certain Class 4 IVDs a full laboratory-based performance evaluation by the TGA.

**How could “In-house” manufactured IVDs be affected by the new framework?**

In-house IVDs are defined by NPAAC (2007; see also TGA 2009) as:

> An IVD that is developed de novo, or developed or modified from a published source, or developed or modified from any other source, or its intended purpose, within the confines or scope of a laboratory or laboratory network. [...] Commercial IVDs being used clinically for purposes other
than that originally intended by the manufacturer are also classed as in-house IVDs.

Laboratories manufacturing in-house tests are currently subject to the NPAAC standard. With the introduction of the new IVD legislation, “in-house” tests that fall within the proposed TGA Classes 1, 2 and 3 for risk will be required to notify the TGA the types of IVDs manufactured in each laboratory for inclusion on a specially designed register. Each laboratory, as part of their NATA accreditation will be required to demonstrate compliance with standard on the validation of in-house IVDs as published by the National Pathology Accreditation Advisory Committee (NPAAC 2007) for each test. Importantly, this standard applies only to in-house IVDs that fall into the proposed TGA Classes 1, 2 and 3.

In-house IVDs that fall into Class 4 are subject to the full current TGA regulatory requirements for HIV and HCV as well as for the future Class 4 IVDs (TGA 2009). The laboratory will need to produce a report on method validation that shows the successful completion of appropriate validation studies for the IVD in question. Laboratories should understand well, that like the TGA’s proposed risk-based classification and assessment framework, the extent of validation of in-house tests should likewise be commensurate with the risks associated with the use and results derived by the IVD. Laboratories are already fully conversant with the NPAAC suite of standards for validation of in-house tests, and for Classes 1, 2 and 3 in-house tests, one would expect that any additional requirements will be satisfied by only minor modifications to the existing QMS within the laboratory.

Importantly, most of the documentation required to satisfy the requirements of the standard will need to cover validation of the in-house IVD.

Validation of an in-house IVD by a laboratory using this standard does not allow that IVD to be supplied as a validated IVD to any other laboratory, unless that other laboratory is part of the same laboratory network, as defined above. For detailed information on the relevant NPAAC standards refer to:


**IVDs for self-testing (home use)**

As defined by the TGA (2008), these are tests that are used at home or in a similar environment and are not supervised by a health care provider (e.g. glucose monitoring). Under the provisions of the proposed regulatory framework, the following self-testing IVDs will not be allowed to be marketed in Australia:

- IVDs used to test for pathogens or diagnose notifiable infectious diseases;
- tests to determine genetic traits;
- IVDs used to test for serious disorders, for example cancer or myocardial infarction.

**Major issues of the proposed regulatory framework**

From the TGA’s perspective, the proposed changes to the IVD regulations are intended to embrace a harmonised framework for risk-based classification and regulation of all IVDs. This “all encompassing” framework is intended to ensure that all tests undergo the extent of regulatory scrutiny that the TGA believes is commensurate with the risk of the IVD thereby enhancing public and personal health.

Whilst the TGA is pushing ahead with its unique regulatory framework, the proposed framework poses a number of significant issues for the pathology industry that will need to be resolved, if implemented in its entirety.

More than 95% of all IVDs are imported into Australia; however, the Australian sponsors or manufacturers may not hold or have readily available sufficient technical or conformity assessment documentation to cover TGA’s requirements. This will be particularly difficult for products that have been supplied to Australian laboratories for more than 20 years now.

The proposed regulatory framework ignores the quality of the results produced by the Australian laboratories and still requires manufacturer evidence that a particular test is safe instead of taking into account existing data (e.g., Royal College of Pathologists of Australasia Quality Assurance Program data and performance of the various tests).

International agreements (such as the Mutual Recognition Agreement) with Europe, Canada or the US are not yet in place for IVDs, so this would require duplication of conformity assessment by the local and international manufacturers.

From industry’s perspective, due to TGA’s 100% cost recovery policy, if not implemented carefully, with due consideration for its original intent to harmonise, streamline and reduce regulatory duplication, the TGA’s proposed framework for IVDs could, unfortunately, increase regulatory burden unnecessarily, increase costs significantly and potentially delay or prevent access to existing or new products to users.

Since the Australian IVD market overall is small, IVD sponsors will need to assess whether the added
regulatory burden and cost to sell their products in Australia is worth the effort. Furthermore, under the transition to the new framework, and as a result of the increased regulatory burden required to enter IVDs onto the ARTG, manufacturers or sponsors may opt to restrict the use of certain products in Australia or change the intended use of their IVDs, in order to fulfill a lower risk classification.

Suppliers of low volume tests and small companies may decide that it is not commercially viable.

For the laboratory, major changes stemming from the new regulations would include the need to “register” in-house manufactured tests and reagents in a specific TGA database and provide the full suite of accompanying validation documentation to NATA prior to gaining ARTG entry.

Conclusions

The reforms for IVD regulation as proposed by the TGA are yet to be finalised or implemented. Overall, the proposed new IVD framework presents the industry with a combination of potential advantages and disadvantages. The move to a risk-based classification and regulatory assessment scheme is a move in the right direction if handled correctly and sensibly. The major disadvantages stem from the increase in regulatory burden and costs to the IVD sponsor or manufacturer resulting in the potential for removal of long-standing pathology tests from the laboratory or a reduction in the introduction of new tests into the market.

Industry has seen how the TGA coped previously with the introduction of the new medical device regulations. Furthermore, the proposed IVD framework is far more complex than that proposed in other countries and more complicated than for devices.

IVDs do pose some significant challenges to the regulator in that they are very different from other medical devices and there is a question of whether the TGA has the expertise or will have enough resources to handle the influx of applications resulting from the implementation of their own far-reaching changes.

It will be interesting to see how the unresolved issues are tackled and how industry and laboratories will adapt to the new system. All of those affected should remain vigilant and carefully assess the potential implications of these changes now.

Ultimately, one hopes that new technology will continue to be made available to Australian laboratories in a timely, sensible and cost-efficient fashion.

References


Therapeutic Goods Regulation 1990 (Commonwealth).
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Late one evening, a full blood count was received from a full-term neonate who had just been delivered by caesarean section. The clinical notes read ‘pallor’. The results from the analyser were as follows:

Hb 64 g/L, MCV 118.9 fL, reticulocyte count 13.4 % (254 x 10⁹/L), WBC 16.2 x 10⁹/L and platelets 278 x 10⁹/L.

A Hb result of 64 g/L is abnormally low for a newborn neonate; the normal range being 121-191 g/L in the above laboratory. A repeat specimen was requested. The Hb was now 60 g/L, confirming the initial result. Whilst the blood film was being stained a direct antiglobulin test (DAT) was performed with a negative result. Both the infant and mother were group O positive and an antibody screen performed on the mother was negative. The total bilirubin was 140 umol/L, (NR 0-150 umol/L).

The infant was transfused with two units of packed cells.

The blood film revealed a nucleated red cell count (NRBC) of 674 NRBC/100 WBC, the normal range being 1-25 NRBCs / 100 WBCs. The blood film image (x 400) demonstrates the markedly increased number of red cell precursors while the blood film images (x 1000) demonstrate marked dyserythropoiesis. Note the nuclear budding and cytoplasmic bridging, classical features of dysplasia.

A differential diagnosis on this infant would include a foetomaternal bleed or less probably congenital dyserythropoietic anaemia (CDA). A Kleihauer test was performed on the mother to check for a foetomaternal bleed. The Kleihauer test was positive; the presence of 3.84 % foetal cells translated to a transplacental haemorrhage of 95.84 mls. Hence the initial diagnosis of a foetomaternal bleed was confirmed.

Some degree of foetomaternal transfusion occurs in approximately 50% of all pregnancies. The most frequently observed causes of occult haemorrhage prior to birth include abdominal or multiple trauma, amniocentesis in the third trimester, post external cephalic version, placental tumours and spontaneous haemorrhages. Haemoglobin values as low as 30 to 60 g/L have been recorded in infants who were born alive and survived.

The clinical manifestations of a foetomaternal haemorrhage depend on the rapidity with which it has occurred. If the haemorrhage has been prolonged, giving the foetus the opportunity to compensate for the anaemia, the infant may manifest only pallor at birth. However, if the haemorrhage is acute, the infant may be pale and sluggish, have gasping respirations and manifest signs of circulatory shock.

The blood film may also be informative. In an acute haemorrhage, the red cells are normochromic normocytic whereas in a more prolonged foetomaternal haemorrhage the red cells may be microcytic and hypochromic. Note that the NRBCs in this case exhibited foetomaternal haemorrhage the red cells may be microcytic and hypochromic. Note that the NRBCs in this case exhibited ragged cytoplasm, a feature seen in iron deficiency. The MCV on this neonate was slightly raised at 118.9 fL, NR (101-117 fL). This was secondary to the significantly raised
The reticulocyte count of 13.4 % NR (4-7 %). In anaemia secondary to a foetomaternal haemorrhage the DAT test is negative and the infants are not jaundiced. The presence of a very high NRBC count is an index of foetal stress.

The diagnosis of a foetomaternal haemorrhage can be made with certainty by demonstrating the presence of foetal cells in the maternal circulation. This is done by performing the Kleihauer-Betke test. The Kleihauer image above demonstrates the presence of acid-resistant fetal red cells on a background of acid sensitive adult red cells that appear as ghost cells. Note that the Kleihauer-Betke method has been replaced by a flow cytometry test for the estimation of HbF in many laboratories.

The infant in this update maintained a stable haemoglobin post transfusion hence a potential diagnosis of CDA was not pursued. Mother and infant went home several days after confinement.

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MARCH 2: Nobel Prize Winner Professor Elizabeth Blackburn Public Lecture “Telomerase and Telomere Biology”, University of Melbourne, Copland Lecture Theatre. 6:00 pm.

MARCH 12: AACB Therapeutic Drug Monitoring’ Scientific Education Seminar, Mater Hospital South Brisbane
www.aacb.asn.au/web/Meetings/

APRIL 30 - MAY 2: SW AIMS 2010 Conference Canberra Rydges Lakeside

MAY 10-12: XXIII International Symposium on Technological Innovations in Laboratory Hematology. The Brighton Centre, Brighton, UK.
www.islh.org/2009/

May 14: AACB ‘PoCT’ Scientific Education Seminar Melbourne, VIC
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JUNE 11-14: AIMS Queensland Tropical Division 25th Annual North Queensland Conference Celebrating 100 years of tropical Medicine in Townsville.

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www.sapmea.asn.au/virology2010

JUNE 26-JULY 1: International Congress of the International Society of Blood Transfusion (ISBT) together with the German Society for Transfusion Medicine and Immunohematology (DGTI), Berlin.
www.isbt-web.org/berlin/

JULY 4-8: ASM 2010 Sydney - Bridging Diverse Cultures. Sydney Convention Exhibition Centre Darling Harbour - Sydney NSW
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AUGUST 23-27: NZIMLS Conference, Bay of Islands.
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OCTOBER 16: ASTH Scientific Workshop, Auckland.

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Questions relating to the Flow cytometry testing for PNH cells at a single referral laboratory during 2009

1. Paroxysmal nocturnal haemoglobinuria (PNH) is a common disorder caused by an acquired genetic mutation of the PIG-A gene.
   True/False

2. Large numbers of PNH cells are rarely found in patients with aplastic anaemia (68% of patients) and myelodysplasia (42% of patients) when high sensitivity is applied.
   True/False

3. PNH is characterised by intravascular haemolysis and episodes of haemoglobinuria which are more obvious at night and early morning.
   True/False

4. FLAER has not replaced the CD59 as the preferred marker on granulocytes and monocytes for PNH.
   True/False

5. In regard to PNH testing it is important to test RBC as well as granulocytes and/or monocytes and also report the clone size. The size of this RBC clone is likely to be reduced due to haemolysis and recent blood transfusion of normal cells.
   True/False

6. The samples tested in this study were EDTA samples.
   True/False

7. True PNH cells display a low CD45 expression whereas immature myeloid cells and myeloblasts may have increased CD24 expression and increased CD45 expression.
   True/False

   True/False

9. A new therapy, involving a monoclonal antibody to complement C5, has recently been released, however this new drug is very expensive and if approved for limited use under the Life Saving Drug Program, extensive clinical and laboratory evidence will be required for each patient.
   True/False

10. The diagnosis of PNH was for many years based on the Ham's test, which showed that PNH RBC are lysed in acidified serum by factors including complement.
    True/False
Questions relating to The changing regulatory environment of in vitro diagnostics- implications for sponsors, manufacturers and laboratory users. Page 9 of this issue.

1. Most diagnostic pathology tests are currently not exempt from any form of pre-market regulatory scrutiny and are only subject to post market monitoring and vigilance by the supplier.  
   True/False

2. Under the proposed new legislation category one is low risk and category four is high risk.  
   True/False

3. IVDs do pose some significant challenges to the regulator in that they are very different and there is a question whether the TGA has the expertise or will have enough resources to handle the influx of applications resulting from the implementation of their own far reaching changes.  
   True/False

4. In general, in vitro diagnostic devices (IVDs) are “pathology tests and their related instrumentation used to perform testing on human samples. Importantly, results from these tests must be intended to assist clinical diagnoses or make clinical management decisions”.  
   True/False

5. Under the current legislative basis for regulation of IVDs, their ARTG status is Registrable, Listable or Exempt.  
   True/False

6. Registrable IVDs, undergo an extensive pre-market review of the product’s Technical File including full safety and performance evaluation by TGA’s sub-contracted reference laboratory in Victoria (NSRL).  
   True/False

7. The TGA want, as part of the new regulatory environment, the adoption of the Global Harmonisation Task Force recommendations. However, to date no other country has adopted these recommendations.  
   True/False

8. Less than 95% of all IVD’s are imported into Australia, however, the Australian sponsors or manufacturers may not hold or have readily available sufficient technical or conformity assessment documentation to cover TGA’s requirements.  
   True/False

9. Listed IVDs are not subjected to an administrative review by the TGA that includes evidence of good manufacturing practice (GMP), instructions for use, details of any human or animal origin material, labelling and promotional material.  
   True/False

10. Increasingly IVDs are also being developed for point of care testing and for home use and many of these are for serious diseases. Again, the TGA believes that current regulation does not provide assurance of public protection in this environment.  
    True/False

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AJMS APACE Questions, AIMS National Office, PO Box 1911, Milton Qld 4064. Facsimile: 61 7 3876 2999
**Color Atlas of Clinical Hematology, 4th Edition**
By A. Victor Hoffbrand, John E. Pettit and Paresh Vyas
Mosby Elsevier, 2009
Hard cover, 544 pages
ISBN: 9780323044530
RRP: AU$295.00

This is the fourth edition of the Atlas, with the previous edition published in 2000. Since that time there have been substantial changes in the classification of many of the haematological malignancies due to the understanding of the molecular basis and molecular genetics of these diseases. This edition aims to incorporate this new knowledge and to update the topics where applicable. The two original authors, A. Victor Hoffbrand and John E Pettit, who are well known authors and experts in the field of haematology, have been joined by Paresh Vyas, who has been responsible for adding the first three chapters on blood formation.

These first three chapters (out of a total of 29 and 527 pages) are titled ‘Cell Machinery’, ‘Cellular Basis of Hematopoiesis’ and ‘Growth Factors’. They are quite detailed and explain the molecular and cellular biology of the cell, how it replicates, the cell cycle, how hematopoiesis occurs, the signalling pathways and mutations that arise. The text is very current with inclusions of paragraphs on the JAK-STAT and RAS pathways and throughout these chapters the illustrations, tables and diagrams are abundant and excellent.

The fourth chapter is an introduction to the ‘Maturation of blood cells and their examination in the peripheral blood and bone marrow’ and describes how the cells are produced and the cellular composition and appearance of each of the cell lines. It also outlines the role of the cytokines in this production and maturation process. Again this is well illustrated with images, tables and diagrams.

The next five chapters deal with erythroid production (or lack of it) covering the different anaemias, genetic disorders of haemoglobin, and iron overload. There are many images of the effects of these disorders on the patients or their organs, and good explanations of how haematenes are incorporated into Hb and how the haemoglobinopathies occur. The images of the blood films are good examples of the disorders and the tables are comprehensive. I am not sure why the authors haven’t included Chapter 17 ‘Aplastic and Dyserythropoietic Anemias’ and chapter 27 ‘Secondary Anemia and Bone Marrow in Nonhematopoietic Disorders’ in this section; some of the disorders covered in the latter are leucocyte derived, but as the following chapters 10 to 16 and 18 to 22 are all about white cells they seem to me to be better placed here.

Benign disorders of phagocytes and lymphocytes, the acute and chronic leukaemias, myeloproliferative and myelodysplastic conditions as well as the lymphomas and myeloma are covered in these chapters. As stated previously, all the images, diagrams and tables are of good quality and informative and illustrate the text extremely well. The section on cytogenetics, immunology, molecular studies, gene arrays and minimal residual disease in the acute leukaemias chapter was both an excellent introduction and update and summary of the importance that these additional tests play in these conditions. I was interested to see the FAB classifications still included - it is a good reference point and comparison to the WHO classification and there may be some readers who are still not familiar with the latter.

Chapter 23 is ‘Tissue Typing and Stem Cell Transplantation’ which is an integral part of the treatment of many of these disorders, and 24 to 26 are the various aspects of haemostasis – ‘Vascular and Platelet Bleeding Disorders’, ‘Inherited and Acquired Coagulation Disorders’ and ‘Thrombosis’. These chapters are very up-to-date with the latest theory and illustrations and diagrams of current tests available in the laboratory.

Chapter 28 is on parasitic disorders and is a brief summary of the major diseases – malaria, toxoplasmosis, babesiosis, trypanosomiasis, filariasis, loiasis, bartonellosis and *Borrelia*. I was a little disappointed that there was no mention of *P. knowlesi* in this section, and also some of the malaria images were not very clear or representative of the individual species.

The final chapter on ‘Blood Transfusion’ was a brief but good overview of the various aspects of this important discipline and once again well illustrated.

This atlas is extremely well compiled, incorporates a vast amount of information and is very well priced. The majority of the illustrations are excellent and really help in the understanding of the more complex text, especially in the molecular and genetic aspects of the various conditions. There are a few minor issues – I noticed that in the legends of two of the images initials and colours were referred to that weren’t there on the black and white image. Also the authors are all English, but American spelling was used throughout the atlas.

The authors stated in the introduction that they “Hope this book will be used as a comprehensive up-to-date illustrated encyclopaedia of blood diseases”. It is an Atlas of *Clinical* Haematology so differs from the widely used morphology atlases that are common in the
haematology laboratory and therefore the target audience is broader than only the medical scientist. I am sure that it will fulfil their hopes and I can thoroughly recommend it for any haematology laboratory, especially in a training hospital.

Robyn Wells
Senior Scientist, Core Haematology
Pathology Queensland Central Laboratory
Royal Brisbane and Women’s Hospital

Diabetes and cancer: Epidemiological evidence and molecular links
Series title: Frontiers of Diabetes Vol.19
By K Masur, F Thevenod, KS Zanker
Karger, 2008
Hardcover, 148 pages
ISBN: 978-3-8055-8640-5
RRP AU$312.00

Diabetes and Cancer: Epidemiological evidence and molecular links is a compilation of papers by leading interdisciplinary experimental scientists and clinicians researching the molecular and clinical features common to multiple chronic diseases. Chronic diseases represent the leading causes of mortality in the developed world, with increasing prevalence associated with changes in lifestyle and habits including reduced physical activity, obesity and poor nutrition choices.

The recent discovery of epidemiological and molecular links between diabetes/metabolic syndrome and cancer originated from interdisciplinary and initially unrelated research into multiple biological processes. The problem with diabetes/metabolic syndrome is that by the time it is diagnosed, most subjects have begun developing chronic disease including cardiovascular disease and cancer. The connection between inflammation and chronic disease such as insulin resistance associated with diabetes and cancer has not been adequately appreciated.

Diabetes and Cancer: Epidemiological evidence and molecular links brings together the collective wisdom of a distinguished group of authors, guaranteeing that this book reports on the forefront of experimental and clinical research into diabetes, cancer and their interconnections. It should be of interest and encouragement to medical scientists and clinicians facing the biggest medical challenge of the 21st Century: to combat the highest predicted mortality diseases – cancer, diabetes and hypertension.

The chapter format is that of a scientific paper, with helpful figures and each chapter is thoroughly referenced. It is not as easy to read as some texts, is more than compensated for by the content. I recommend this volume to researchers in the field of metabolic syndrome and to those interested in lifestyle medicine. The connection between nutritional inadequacy and diabetes and cancer is emphasised providing valuable interventional options to the attention of dieticians and nutritional researchers. Multidisciplinary researchers will also appreciate reflecting on the different aspects of the two linked disease and that the only possible chance of finding an early curative therapy is by combining the approaches of specialists across different fields.

Dr Bevan Hokin (Director of Pathology), and Dr Fay Chambers (Pathologist)
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Wahroonga, New South Wales

Mosby’s Diagnostic and Laboratory Test Reference
Kathleen Deska Pagana and Timothy J Pagan
Karger, 2007
Soft cover, 1104 pages
ISBN: 9780323053457
RRP: AU$ 87.00

Well, I was impressed. Not awed, but impressed. At over 1000 pages, this handy reference guide lists hundreds of tests, and provides a summary of pertinent information for each of them. Tests included are pathology tests, electro-diagnostic tests, x-rays, endoscopy, ultrasound and nuclear scans. The main text comprises an alphabetical listing of each test that begins on a new page and follows a set formula, namely ‘Name of test’, ‘Type of test’, ‘Normal findings’, ‘Possible critical values’, ‘Test explanation and related physiology’, ‘Contraindications’, ‘Potential complications’, ‘Interfering factors’, ‘Procedure and patient care’, ‘Abnormal findings’ plus an additional space for notes. I scanned through each test entry, but naturally more thoroughly checked the entries related to my specific field of haemostasis. The latter part of the book lists tests under other headings, such as ‘By body system’ (i.e., cancer studies, cardiovascular system, endocrine system, gastrointestinal system, haematological system, etc), by ‘type of test’ (i.e., blood tests, electro-diagnostic tests, etc), and by ‘disease and organ panel’ (i.e., anemia, coagulation screening, DIC, etc). At the end of the book is the mandatory index, in case you still have trouble finding what you are looking for.

The authors, a doctor and a nurse, have a breadth of knowledge that impressed me. The authors have the same surname, suggesting a husband and wife team, or perhaps siblings. This book is a general text, and the level of specific knowledge presented for each test appears to be extensive. Perhaps this is reflective that as the ‘ninth edition’, several iterations have been developed over time. This is not to say that no errors or holes exist in this book;
there are some of these, but most of the text related to tests with which I am familiar is fairly accurate and is also up to date.

Some examples related to errors and omissions include: occasional incorrect page reference cited; lists the test ‘Anticardiolipin antibody’ and indicates that this test is positive in some patients with systemic lupus erythematosus (SLE), and also identifies an association with ‘Antiphospholipid Syndrome’, but then later fails to list ‘Antiphospholipid Syndrome’ as a possible cause of test elevation; lists the coagulation factors, and identifies factor XI within the text, but then omits factor XI from a key summary table; identifies increased factor VIII within the context of acute inflammatory reactions, but then fails to identify the same context for von Willebrand factor (i.e., instead incorrectly states that elevation of von Willebrand factor is not associated with any common disease state); does not yet recognise the association of elevated factors including factor VIII with increased thrombosis risk; provides a reasonable summary for fibrinogen, but then talks about fibrinogen ‘serum levels’; doesn’t mention dysfibrinogenemias as a possible cause of lowered fibrinogen; mentions that factor XI deficiency and antiphospholipid antibody are two major abnormalities identified in pregnant patients with a prolonged for the activated partial thromboplastin time (APTT), and then states that “These coagulopathies are not usually associated with excessive bleeding or thromboembolism”; provides a reasonable summary regarding platelet aggregation testing including the recognition that many drugs may ‘interfere’ with test results, but then fails to list ‘medication’ as a possibility for abnormal findings (when it is instead often the main culprit for an abnormal test result); provides a variable normal reference range for all the listed coagulation factors (thus recognising that these ranges are not just a ‘standard’ value of 50-200% for all), but then fails to identify that these ranges may differ between laboratories (notably, on occasion other tests carry this ‘warning’); and did I mention that ‘von Willebrand factor’ is not listed as a test in this manual?

On the other hand, as I have already mentioned, the breadth and currency of knowledge is impressive. Some examples are: recognition and a reasonable summary of primary and secondary haemostasis and fibrinolysis; recognition that recombinants for factors VII, VIII, IX and XIII are available for therapy; recognition that elevated D-Dimer is a risk factor for thrombosis recurrence; recognition of some limitations with thrombophilia testing, including factor V Leiden, and some recommendations for who and when to test, including a key recommendation that such testing should be accompanied by genetic counselling; a reasonable summary of information for the PFA-100 (‘closure time test’); clear recognition of the interferences and false positives possible for Proteins C and S; recognition of genetic variants influencing warfarin sensitivity for the prothrombin time test (or the International Normalised Ratio, INR).

I know that the prior paragraph containing examples of ‘errors and omissions’ is indeed longer than that dealing with ‘the breadth and currency of knowledge’, but in reality, most of the former ‘errors and omissions’ reflect minor issues, whereas the latter generated a clear positive impression in my mind that largely overcame the issues identified for the former.

Another potential problem to be aware of is that the book is clearly US-centric. There are several tests included that would be rarely performed in Australia, and some old tests are listed that would no longer be performed here. Also, some tests which are clearly more invasive or ‘prohibitively’ more costly than others are sometimes treated in a similar casual manner. This may become a problem in certain situations, for example when the guide is used by a training doctor, who may unwittingly order a comprehensive panels of invasive/costly tests that experienced doctors would less likely request. But, in the end, I would still identify this as a great general reference book.

So, more specifically, how useful will most members of AIMS find this book? To some extent, this depends on where you work. The book could be useful for those of us who specialise in one area but may also sometimes need to know a little about other areas. For example, I would see some value in having a copy of this kind of text available within most Pathology departments, or at least in the specimen processing areas, as a quick and easy reference. Nevertheless, it is also important to recognise that the text is clearly intended as a kind of pocket guide for doctors and nurses. You would, however, need a large pocket I guess, as the book measures 115x190mm.

In conclusion, at under $100, you could do much worse than purchase this book for your laboratory. If this is too much to spend, my alternate recommendation would be to use the RCPA test manual, freely available at <http://rcpamanual.edu.au/>. Unfortunately, printed editions of the RCPA test manual are no longer available. Also important to note is that test information for many tests was last updated over five years ago, so test currency may also be a problem. On the other hand, the RCPA test manual is freely available, Australian focussed, and I would be remiss not to say it – does list von Willebrand factor (in its many test forms).

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The initial impression of *Chromosome Structure and Function* was “nice looking book”. It is a hard cover and durable. The page numbering was initially odd, but you quickly recognise the book is a reprint of *Cytogenetic Genome Research*, vol. 124, No. 3 - 4, 2009. The editor has several publications and appears to have an interest in the interactions of histone H3 in plants. The editor provides a well constructed summary of the book in the preface.

The book is easy to follow although no formal chapter construct is used and its contents are divided into review and original articles, which are clearly marked at the beginning of the article. Tables and pictures complement the articles. The majority of articles are related to studies of plant chromosomes and genome expression. Other topics studied involved stem cells, insects and mammalian chromosomes.

To outline a few topics of interest, in recent years telomeres have attracted some attention due to the protective role they have in chromosome stability. The very first article provides an insight into telomere role during meiosis of *Arabidopsis thaliana* (a flowering plant with a small genome that has a rapid life cycle) and the future possibilities of live imaging techniques in further understanding of telomere behaviour. An original article explores the function of centromere ultrastructures using high resolution field emission scanning electron microscopy. This includes excellent images of chromosome structure.

Double minutes and chromosomal homogenous staining regions are examined in a review article, page 126. It discusses the possibility of how these elements may alter chromosome structure and function, this is particularly relevant in the clinical sense as these extra chromosomal structures can be seen in some cancer cell lines. An original report on the use of multi colour FISH and Quantum dots is also provided, concluding that there is more potential for use with gene mapping of specific gene loci using 3D imaging with high resolution 4Pi laser confocal microscopy.

*Chromosome Structure and Function* seems to be aimed as a tool for the advanced student in molecular biology or cytogenetics / molecular scientist continuing in a research role in chromosomes and postgraduate studies.

Karger also have this journal online with ready to conduct topic searches, pay as you go, of course.

Vince Hale MAIMS
Scientist
CaSS Pathology Queensland
RBWH HERSTON Queensland

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**Hematopoietic stem cell transplantation in clinical practice**

By Jennifer Treleaven & A. John Barrett
Churchill Livingstone (available through Elsevier Australia) 2008
Hard cover, 555 pages
ISBN: 9780443101472
Online Price: AU$ 265.50
RRP: AU$ 295.00

Haematopoietic stem cell transplantation, a relatively new treatment modality having been used clinically since only the 1970s, is rapidly developing into a highly effective treatment for a broad range of haematological, immunological, metabolic and malignant diseases. Haematopoietic transplantation is now curing many conditions that would previously have been fatal – and the potential for future progress is almost unlimited.

*Haematopoietic stem cell transplantation in clinical practice*, in a most readable format, effectively summarises the progress of ongoing clinical and transplant research involving haematopoietic transplantation. More importantly the latest research is presented within the context of clinical issues faced in practice. The volume is divided into six major sections with contributions from around 80 of the world’s ‘Who’s who’ in the field. The history of haematopoietic transplantation and its biology is reviewed. Current considerations for the clinical use of stem cell transplantation are presented and its role versus alternative forms of treatment is discussed in a balanced manner. Important practical information is also presented regarding the organisation and operation of a clinical stem cell unit along with ethical considerations faced in practice.

It is acknowledged that advances in the field have occurred so rapidly that it is difficult to keep abreast of all the changes. A regular review and update is therefore necessary – one of the stated objectives of this book. Advances in all fields of transplantation are discussed, with a thorough overview of the literature included. One of the major appeals of Haematopoietic Stem Cell Transplantation in clinical practice is the inclusion of
hundreds of photographs, illustrations, tables and lists. These tables assist the reader to review and assess options rapidly and effectively.

Haematopoietic stem cell transplantation in clinical practice will appeal to and be a valuable resource to all healthcare workers in the field of haematopoietic transplantation, medical, scientific and nursing staff and including those with day-to-day responsibility for patients. It is highly recommended.

Dr Bevan Hokin, Director of Pathology, Sydney Adventist Hospital Wahroonga, New South Wales Cairns Base Hospital Cairns, Queensland
BOOKS FOR REVIEW

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.

Requests to: Australian Institute of Medical Scientists, PO Box 1911, Milton, Qld 4064.
Tel: (07) 3876 2988. Fax: (07) 3876 2999. Email: aimsnat@aims.org.au


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AIMS has initiated a scholarship programme for the RCPA/AIMS Morphology Workshop.

In 2010 there will be up to TWO scholarships available for all financial members of the Institute. Both will be for the workshop held on 23-24 July 2010, at Australian Technology Park in Redfern, Sydney.

This workshop has been held at least twice a year for the last 18 years. It is organised through the RCPA QAP in Haematology office by a group of AIMS members and Haematologists. The workshop is now acknowledged as the premier workshop of its type, not only in Australia but also in the Asia Pacific Rim. It is a ‘wet’ workshop held over two full days.

CONDITIONS

Applicants would be expected to have some basic knowledge and the scholarship is particularly suitable for members who either do not have resources for continuing education available to them or have a need for retraining due to rationalisation or multiskilling in their workplace.

Previously unsuccessful applicants are encouraged to apply.

VALUE

The value of each scholarship will not exceed $1000. The exact value will depend on the applicant’s travel requirements.

DEADLINE

Friday 16 April 2010

SEND TO

AIMS National Office
PO Box 1911
MILTON QLD 4064
Phone: 07 3876 2988
Fax: 07 3876 2999
Email: aimsnat@aims.org.au

Application forms available online at

Application Form
AIMS/RCPA Blood Cell Morphology Workshop
AIMS Scholarship

Name: ____________________________ Membership No: _____________

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☐ My resume detailing my place of work, qualifications and employment history is enclosed.

In 50 words or less, please explain why you believe you should receive the scholarship:

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Four scholarships of $1,250 each will be offered to financial members of AIMS in 2010 to support attendance at the National Scientific Meeting.

Two awards of $1,000 will be offered for first-time presenters at the National Scientific Meeting, one for an oral presentation and one for a poster.

Applicants must be current members of AIMS and must have held membership for at least six months at the time of the application. Affiliate, retained or student members are not eligible to apply. For full details and application forms see the AIMS website www.aims.org.au or contact National Office.

Closing date for applications: 14 May 2010
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 January 25th, 2008.

Manuscripts that do not fully comply with the following ‘Instructions to Authors’ may be returned for revision before they are considered for publication.

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.

Papers published in the AJMS are in the form of:
- Review Articles
- Original Articles
- Brief Communications
- Technical Notes
- Case Studies
- Letters to the Editor
- Book Reviews

Articles submitted for publication are understood to be offered only to the AJMS and those accepted become the property of the AJMS.

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.

Requirements and preparation of manuscripts

General

Articles should be submitted in electronic format to ajms@aims.org.au. If an article is too large to be submitted by email, it should be submitted on a CD.

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/website%20stard/). The principles outlined in these standards may be used as general guidelines and not just as applied to clinical trials and diagnostic studies.

Title Page

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/meshhome.html). 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
- References

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; lead 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.

Results

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.

Discussion

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)…

(ii) It has been successfully demonstrated that ...(Smith and Brown 1981; Auteur 1995; Scienziato et al 2007).

(iii) Following further investigation, Wetenschapper (2002) highlighted the difficulties inherent in...

Where there are three or more authors, acknowledge only the first author, e.g. (Smith et al 2007). For two authors the following style should be used (Smith and Brown 2007).

The reference list should be in the format described below journal titles should be abbreviated in Index Medicus format (see: ftp://nlmpubs.nlm.nih.gov/online/journals/ljiweb.pdf ) using standard abbreviations from the ISSN List of Title Word Abbreviations (see: http://www.issn.org/en/node/344) All authors should be given in the reference list.

Do not use abstracts as references. “Unpublished observations” and “personal communications” may not be used as references, although references to written, not verbal, communications may be cited (in parentheses) in the text. Include in the references manuscripts accepted but not yet published, designate the journal followed by “in press” (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as “unpublished observations” (in parentheses).

Examples of the correct form for references are given below:

i) Journal Reference:


ii) Personal Author(s) of a book:


iii) Editor, Compiler, Chairman as Author:


iv) Chapter in Book:


v) Online documents:


Tables

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.

Legends for Illustrations

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.

Abbreviations

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

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

<table>
<thead>
<tr>
<th>Abbreviation or Symbol</th>
<th>Standard Units of Measurement</th>
</tr>
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<tbody>
<tr>
<td>g</td>
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<tr>
<td>g</td>
<td>gravity</td>
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<td>Newton</td>
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<td>nanometre</td>
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<td>revolutions per minute</td>
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</tbody>
</table>

### Additional Information

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

A new day dawns in Cellular Analysis

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