Idiotic or Idiopathic Cold Agglutinin Disease
Autoimmune Haemolytic Anaemia (AIHA) can be broadly categorized into four types. These are:

- Warm autoimmune haemolytic anaemia (WAIHA)
- Cold Agglutinin Disease (CAD)
- Paroxysmal Cold Haemoglobinuria (PCH), and
- Drug-induced haemolytic anaemia
Transfusion Folklore

Anecdotal evidence suggests that AIHA patients will present to your Emergency Department:

Simultaneously with a multiple gunshot victim, or
On the night of the State of Origin decider, or
When you are on-call
These four types of AIHA can be differentiated by laboratory findings together with clinical history. These laboratory results can be summarised in the following table.
# Laboratory results in AIHA

<table>
<thead>
<tr>
<th>Type of AIHA</th>
<th>Red cell screen</th>
<th>DAT</th>
<th>Eluate</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIHA</td>
<td>Positive</td>
<td>Positive (IgG+C3d)</td>
<td>IgG</td>
<td>Rh, LW, Kidd</td>
</tr>
<tr>
<td>CAD</td>
<td>Positive</td>
<td>Positive (C3d)</td>
<td>Nil</td>
<td>I, i, rarely Pr</td>
</tr>
<tr>
<td>PCH</td>
<td>Positive</td>
<td>Positive (C3d)</td>
<td>Nil</td>
<td>P</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Positive/Negative</td>
<td>Positive (IgG+C3d)</td>
<td>IgG/Nil</td>
<td>Drug</td>
</tr>
</tbody>
</table>
Background

WAIHA

Idiopathic
Secondary (to lymphoma, CLL, SLE and other autoimmune disorders and Transplantation)

Clinical picture is extremely variable due to the different underlying diseases and the ability of the marrow to compensate.

CAD

Idiopathic/chronic (recognition of secondary disease increases over time)

Secondary (lymphoproliferative disorders)

Acute/transient (infections, especially Mycoplasma pneumonieae and EBV)

Clinical picture may include intravascular haemolysis and haemoglobinuria. No fever, chills or renal insufficiency reported
Background

PCH (biphasic haemolysin)
Acute/transient (mainly in children after a variety of infections with little if any cold exposure)

Chronic (congenital syphilis with acute episodes of haemolysis after cold exposure)

Clinical symptoms include fever, chills, back pain and occasional transient renal failure

Drug-induced
Several mechanisms involved depending on the drug under investigation (a subject on its own)

Some of the drugs that may cause AIHA are: Penicillin, a-methyldopa, NSAID, and cephalosporins
Female (RH) born on 04/05/1945 in Afghanistan presented at Blacktown emergency department on 16/10/2002
Symptoms included lethargy and jaundice
FBC, LFT, group and screen requested
FBC and film suggestive thalassaemia with autoagglutination present
Repeat pre-warmed (37°C) FBC and film improved MCHC and removed autoagglutination
LFT revealed a raised bilirubin
Initial group showed discrepant reactions
Red cell antibody screen positive (throughout)
Recollection and separation at 37°C for G&S
Pre-warmed tube group successful
Pre-warmed/warm-washed tube IAT(IgG) screen and panels clear
Warm-washed DAT positive(C3d)
Ether elution negative
Cold agglutinin titre (saline) of 64  at 4°C  against adult and autologous cells
Hb EPG confirmed heterozygous beta thalassaemia
Patient discharged without treatment or follow-up tests
Subsequent presentations

08/07/2006
Recollection and separation at 37°C required for G&S and extended phenotype
Investigation into aetiology of her disease at this time concentrated on infectious causes, including:

Mycoplasma, Influenza A and B, parainfluenza 1,2 and 3, RSV, HIV, Legionella, TB and Pneumocystis carinii. All proved negative

17/10/2007
Cold agglutinin titre increased to 512 with same specificity

06/09/2010
Flow cytometry provided no evidence of B-cell lymphoproliferative disease. Normal serum EPG
Subsequent presentations

03/02/2012
Cold agglutinin titre increased to >2048 at 4°C

28/06/2012
Hb=52 and symptomatic
Transfused 4 red cells; partial incremental increase in Hb(60s). Hb remains stable through July and August

05/09/2012
Hb=55 and symptomatic
Transfused 3 red cells; increase of Hb(80s). Hb remains stable in October. Patient discharged without further transfusions
**Conclusions**

Persistent autoimmune antibody present for 10 years

Reactions indicate a preference for 4°C with a specificity against the “I” antigen

DAT is C3d positive with a negative ether elution

No underlying disease state detected (infectious or lymphoproliferative)

Collection, separation and testing at 37°C provides accurate immunohaematology results

These facts confirm the diagnosis of idiopathic/chronic CAD
Patient advised to keep warm and avoid cold drinks

Drug treatments include chlorambucil and cyclophosphamide with varying success
Glucocorticoids and splenectomy are generally not effective

Red cell transfusion should be limited to patients with compromised cardiovascular systems

Additional supply of complement components via transfusion should be avoided (washed RBCs?)

Infusion should always be performed through a blood Warmer
Periodic screening by flow cytometry and serum EPG recommended
Most presentations by RH occurred during winter or early spring
Investigation of infectious agents performed 4 years after first presentation (therefore of limited value)
Over time, the cold agglutinin titre increased from 64 to >2048
The patient required red cell transfusion for the first time in 2012 (full increments were not achieved)

Does this indicate a progression in her disease, or an increase in cold exposure, or improved blood collections at 37° C minimising autoabsorption?