

Package deal

HAEMATOLOGY IS THE PERFECT CAREER FOR DOCTORS WHO CAN'T CHOOSE BETWEEN DETECTIVE STORIES AND HOSPITAL BEDSIDE DRAMAS. WRITE JENNI HARMAN AND MICHIKO SMITH.

PHOTOGRAPHER: EAMON GALLAGHER AND BRETT HARTWIG



Seven-year-old “Will” just wanted to kick a ball around with his mates, but since starting treatment with the anti-clotting drug warfarin, he had been sidelined from ball games, tree-climbing and all pursuits that might risk a potentially disastrous bump.

Will had been diagnosed with a deficiency of protein S, a naturally occurring anticoagulant necessary to prevent abnormal blood clotting occurring

within a blood vessel. In Will’s case, insufficient levels explained the worrying stroke-like symptoms he had been showing.

Unfortunately, the standard anticoagulant treatment carries the opposite risk of fatal bleeding – perhaps acceptable to a sedate adult, but extremely frustrating to a 2018 World Cup hopeful.

Even more frightening for Will and his parents, he was still considered to be at risk of another stroke when referred to Professor Paul Monagle, paediatric haematologist at the Royal Children’s Hospital, Melbourne. On careful re-analysis, Professor Monagle found that Will’s blood level of protein S was in fact normal for his age, and was low only relative to standards derived from studies in adults.

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Professor Monagle’s investigation led to the discovery that Will’s neurological episode hadn’t been a stroke at all, but a treatable seizure. With warfarin no longer necessary, Will is now catching up on two years’ climbing and kicking and generally getting his knees as scabby as the next kid’s.

For other children, strokes and once-rare vascular diseases are a reality. The Royal Children’s Hospital sees an average of one child every week with thrombosis (clotting accidents) and at least one each fortnight with a stroke.

As improving medical care means that more children are surviving once-fatal primary illnesses, blood clots from central venous catheters inserted into the chest are becoming more common. For pathologists, this change has opened up new areas of investigation.

“Research into thrombosis in children is fascinating because we have such little background knowledge,” Professor Monagle says.

“Although all the same coagulant molecules are present in children and adults, they are present in different quantities. This means that the entire mechanism by which clots are formed is different in children compared to adults. The medical consequence of this is that anticoagulant drugs that were effective in adults may not be similarly effective in children.”

As this understanding advances, tailored treatment is replacing the former “one size (adult size, that is) fits all” approach.

“How you devise the treatment plan for a three-year-old is completely different from a treatment plan for a 10-year-old,” Professor Monagle explains, citing this as one of the aspects of paediatric haematology that keeps the job both challenging and interesting.

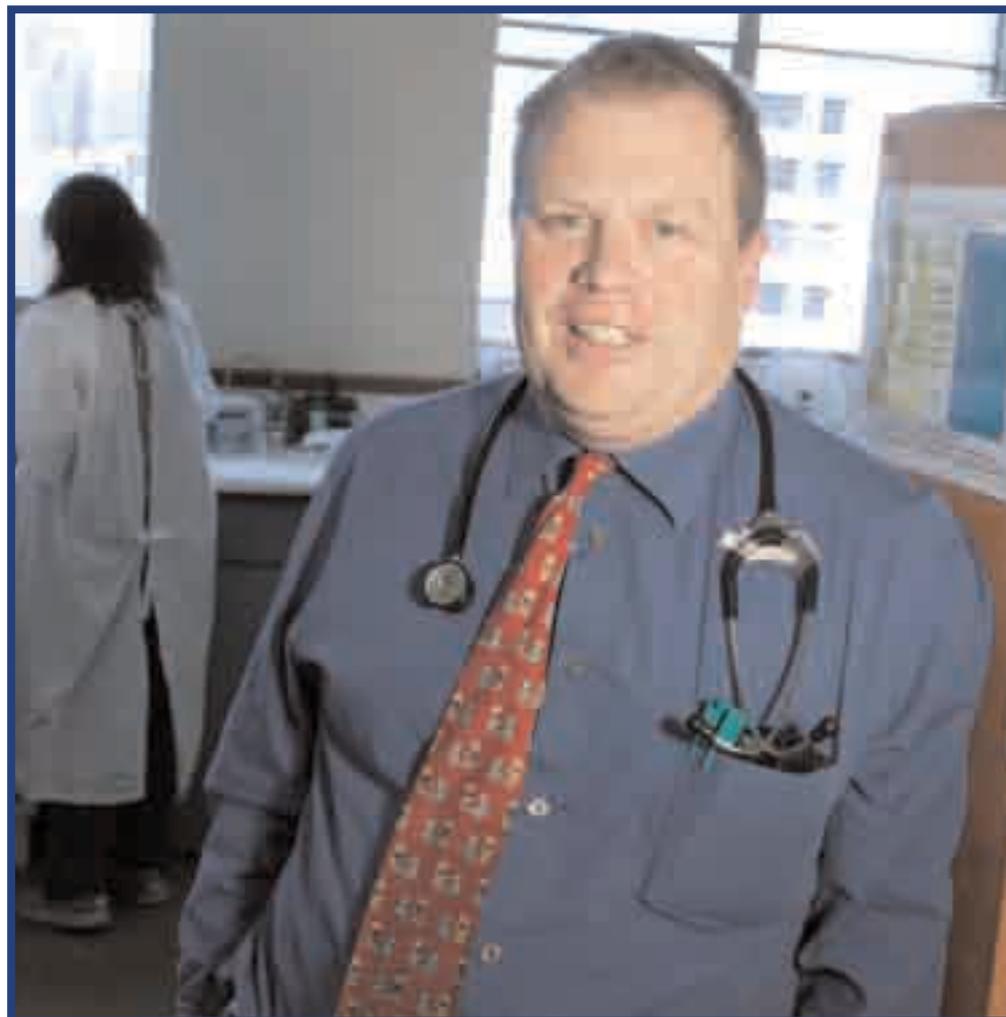
With better care, better anticoagulation management and better education for the children’s families, complications and recurrences of thrombosis are now extremely rare.

Professor Monagle arrived at a career in thrombosis research via training in paediatrics, during which he became interested in childhood cancer and decided to put in a year in a haematology laboratory as part of the groundwork for a job in oncology. To his surprise, he thoroughly enjoyed the “detective work” he found himself engaged in and decided to switch to paediatric haematology.

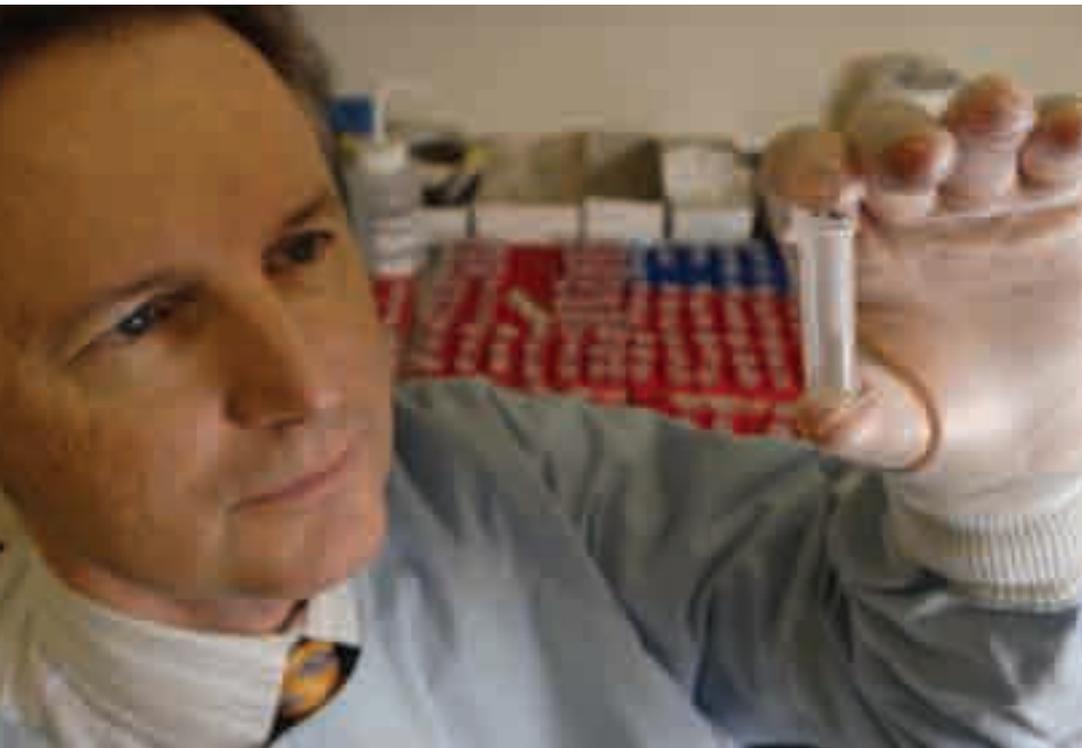
“Not a week goes by where you are not faced with a patient with a new disease you haven’t previously treated,” he says.

Professor Monagle now heads the department of pathology at the University of Melbourne, where he leads a research team investigating developmental haemostasis – the way the complex biochemistry of blood clotting changes throughout childhood – a new understanding that has led to the adjustment of laboratory testing procedures to ensure misunderstandings such as in Will’s case do not happen in future.

What is exciting about haematology, Professor Monagle says, is the chance to be involved in all stages of a patient’s



Professor Paul Monagle, paediatric haematologist at the Royal Children’s Hospital, Melbourne



Professor Tim Hughes, director of haematology research at South Australia's Institute of Medical and Veterinary Science

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care, avoiding the compartmentalisation imposed by other medical specialities and enabling a “multilayered” approach.

“As a clinician, you have the opportunity to follow a patient right through from presenting problem and diagnosis to treatment. This allows the clinician to devise the best treatment, often along with consultants from other specialties, and follow through with the patient.

“Diagnosis and treatment of clotting disorders requires paediatric haematologists to work with consultants from many different specialties. The collaboration with consultants of various fields adds to the breadth and variety of

work a paediatric haematologist faces on a daily basis.”

This breadth of focus is also what drives Professor Tim Hughes, director of haematology research at South Australia's Institute of Medical and Veterinary Science.

“The attraction of haematology for me was the capacity to continue an active clinical practice and delve into the molecular and cellular biology of a disease.

“I can see a patient with leukaemia, take their blood or bone marrow cells, follow through to the lab and study these cells in culture. And then take this improved understanding of the leukaemia back to the patient to devise the best treatment plan,” he says.

“Haematology is rare among medical professions, allowing you to couple fundamental research with clinical practice.”

Professor Hughes moved into haematology in the late 1980s, at a time when researchers were pinpointing the precise structure and actions of the aberrant enzyme responsible for malignant overproduction of white blood cells in patients with chronic myeloid leukaemia (CML).

The CML story highlights the interaction between laboratory and clinical medicine that so fascinates

haematologists. In the 1960s it was understood that this usually fatal disease was caused by a chromosomal abnormality and by the 1970s, improved genetic research techniques revealed that this abnormality involved the fusion of two genes.

The '80s saw the protein product of this cancer-causing double gene (known as *BCR-ABL*) identified as an altered, overactive form of the tyrosine kinase enzyme. During the '90s researchers focused on finding molecules shaped to lock into the abnormal enzyme and block its action. By the late 1990s they succeeded with the enzyme inhibitor imatinib mesylate (Gleevec), a treatment considered to have revolutionised the management of CML.

“It is a perfect example of understanding the fundamental mechanism of a disease and following it through to therapy. There is rarely a disease where you can follow through from cause to therapy as directly as for CML,” Professor Hughes says.

“The risk of progression from chronic to acute leukaemia before the availability of imatinib was about 15 per cent per year. The risk for patients on imatinib therapy was about 3 to 4 per cent for the first few years of therapy and has now fallen to less than 1 per cent. Based on this, we can project survival of better than 15 to 20 years for most patients – compared with only four to five years

Becoming a haematologist

Medical graduates who have completed their internship in a hospital are eligible to apply for a training position in haematology. The minimum time for specialist training is five years, in a registrar position accredited by the Royal College of Pathologists of Australasia.

Trainees can choose either to train solely for the RCPA qualification or, after qualifying as a Fellow of the RCPA, train for a dual fellowship with both the RCPA and the Royal Australasian College of Physicians (RACP)

before imatinib,” Professor Hughes explains.

“There are now over 1,000 patients living full and productive lives on continuous imatinib therapy. As well as having a dramatic effect on survival, the quality of life for patients on imatinib is generally excellent. The previous best therapy, interferon, was associated with major side effects which limited recipients’ quality of life.”

The chase is not over yet, though. Lack of response to treatment in some patients and the development of resistance by the leukaemic cells led to the development of a new generation of these drugs, now undergoing clinical trials. A mutation recently identified by Professor Hughes’ research group produces a CML-inducing protein that is resistant to all available enzyme inhibitors.

“Resistance can occur when a small population of the CML cells carry a mutation in the *BCR-ABL* gene fusion, which is not inactivated by imatinib. As you continue to treat with imatinib you ‘select’ for more resistant cells as the susceptible cells die off.

“We were able to identify a specific type of mutation (called ‘p-loop’) which was associated with a particularly poor prognosis. Based on this knowledge, we have been able to rescue patients who develop these p-loop mutations with a donor stem cell transplant before they have developed advanced disease. This finding has now been confirmed in French and Italian studies, and has changed the way these patients are treated internationally.”

Given that imatinib acts only against leukaemic cells already in the circulation, Professor Hughes and his group are now turning to their precursors, trying to discover better ways to target leukaemic stem cells.

Professor Hughes says the key to good research is to find great collaborators.

“Australian haematologists are well known internationally for their capacity to conduct high-quality clinical research and combine different fields of science through collaboration. The Australasian Leukaemia and Lymphoma Group is recognised in particular, because the group’s haematologists and scientists build such strong collaborations.”

The case for cases

Research into bleeding disorders, and the evolution of haematology as a distinct discipline, has advanced through careful case-by-case observations by clinicians fascinated with the diversity of medical outcomes. The present-day catalogue of coagulation and anticoagulant factors was pieced together largely through the detailed study of individual patients.

Haematology is still suited to those who like to follow an individual’s case story right through – doctors for whom puzzling over an idiosyncratic response to standard treatment is what makes medicine fascinating, rather than seeing those cases as exasperating aberrations in an otherwise tidy array of textbook outcomes.

Some argue we need to ensure that this type of thinking isn’t lost in an era where large, randomised, controlled clinical trials and meta-analyses (statistical analysis of data from multiple trials) are sometimes seen as the only respectable evidence.

As UK haematologist Paul Giangrande points out: “It can be difficult in this intellectual climate to appreciate that humble case reports, usually banished to the last pages of modern journals, have often been the source of great advances in the past. In particular, many of the advances in coagulation medicine have come from case reports from physicians who have written about patients encountered in their busy everyday practice, patients in whom they recognised something special or unusual, and from whom they have learnt important clinical and scientific lessons.”

Source: Paul L. F. Giangrande. Six characters in search of an author: the history of the nomenclature of coagulation factors. *British Journal of Haematology* 2003; 121: 703–712.

One area in which Australian haematology enjoys a position at the forefront of research is multiple myeloma, another white blood cell malignancy. In multiple myeloma, abnormal plasma cells crowd the bone marrow and block the production of normal blood cells, suppressing the immune system and causing kidney failure and painful bone damage. About 1200 Australians are diagnosed with multiple myeloma every year, typically aged in their early 60s.

The current standard treatment for patients under 65 is stem cell transplant using the patient’s own cells harvested from the blood. This is usually attempted after three to six months’ treatment trying to reduce the tumour load and prevent stem cell contamination with malignant plasma cells. Some patients undergo a second transplant following relapse of the disease some months after the first. However, newer approaches that target the malignant cells might change this practice in the near future.

“There have been tremendous improvements in drugs to treat multiple

myeloma,” says Professor Douglas Joshua, head of clinical haematology at the Sydney Cancer Centre.

Targeted treatments available in North America and now undergoing clinical trials in Australia include bortezomib, a drug that kills cancer cells by inhibiting a protease enzyme. Thalidomide’s reputation has also enjoyed a recent rehabilitation following the discovery that, when combined with other cancer treatments, it is an effective drug even in patients who have relapsed following other treatments.

According to Professor Joshua, haematology is a career choice that will ensure a young doctor a part in the next generation of medical breakthroughs.

“If you want to be at the forefront of development of new techniques, you want to be in haematology,” he advises.

“Haematology is very exciting because it encompasses both laboratory science and clinical practice. If you want the total package of laboratory research and clinical practice, then you should specialise in haematology.” 🔥