NZIC Chemistry IN NEW ZEALAND

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The Cover

Cover photography by Matt Walters, School of Biological Sciences, University of Canterbury

New Zealand Institute of Chemistry

supporting chemical sciences

July News

Comment from the President

One of the rewarding aspects of the role of President of the Institute is the opportunity to visit each of the Branches to meet with the members and deliver a lecture. At the time of writing I have made two visits, the second of which was to the Wellington Branch which, naturally, I know quite well. The first was to Manawatu where I spent a very pleasant and informative day at New Zealand Pharmaceuticals as the guest of Dr *Ghislaine* ***Cousins***, and at Massey University, hosted by Dr *Mark* ***Waterland***. Both visits were very encouraging: at Massey I was able to discuss research and teaching with several of the new staff that have been appointed in the last few years. Issues included the difficulties of balancing a heavy teaching load against the need to produce research outputs for the next Performance Based Research Fund assessment in 2012. Despite some evident problems, there was a general air of optimism with several research projects producing interesting results. I was particularly interested in the development of a new student-centred approach to teaching chemistry in the laboratory that challenges first-year students to think analytically about scientific problems.

NZP offered quite a different, but equally encouraging perspective on chemistry in NZ in 2009. The company occupies a valuable niche in the international market for speciality chemicals and has been able to invest in new production facilities in recent years (as reported in this *Journal*). One of the many positive aspects of the NZP operation is the synergy that exists between the company, IRL and several NZ universities, to the advantage of all. I am looking forward to visiting the other four Branches later in the year.

As I write this, the Government's 2009 Budget is fresh in my mind. We were well primed to expect little but, under the circumstances, science and education fared better than some. Although the main news media did not devote much space to science spending, the Treasury and other government websites carry the essential detail. A good deal of the positive funding news is really just a redeployment of monies and the budget disguises real losses in funding, notably the scheme to allow R&D tax credits. However, there is some welcome news in the increase in Capability Funding for the Crown Research Institutes and the extra $9 M for the Marsden Fund each year for the next four years, the latter being an increase of more than 20% on current funding. This might mean one extra funded project in chemistry each year. Against that, it appears that the Top Achiever Scholarships for the best of our PhD candidates are destined to follow the Enterprise Scholarships into oblivion. A new scheme to fund summer research students in universities is welcome as is the Prime Minister's Science Prize. Overall, there is little to raise NZ from its modest position on the OECD ranking for investment in research and development and, lest we become too pleased with our lot, Bill English left us with a pessimistic outlook for budgets to come.

On a more positive note, you will be aware that 2011 has been designated the International Year of Chemistry by the United Nations. This will be a ***time to celebrate the achievements of chemistry and its contributions to the well-being of humankind***. IUPAC and UNESCO envisage that the activities associated with the year will:

- increase the public appreciation of chemistry in meeting world needs
- increase interest of young people in chemistry
- generate enthusiasm for the creative future of chemistry
- celebrate the 100th anniversary of the award of the Nobel Prize in Chemistry to Marie Curie and the 100th anniversary of the founding of the International Association of Chemical Societies, a predecessor of IUPAC.

The NZIC, in collaboration with RSNZ, will play a prominent part in the celebration at the national and regional level. Council is discussing some of the ways we can contribute, and a publication to follow *New Zealand is Different: Chemical Milestones in New Zealand History* is one possibility that is being considered. I hope the Branches will also be considering appropriate ways to mark the Year of Chemistry in their regions. Please write to me if you wish to suggest a way the NZIC can celebrate IYC.

John Spencer

President

Farewell

This is the last issue of *Chemistry in New Zealand* for joint Managing Editor Fiona Summerfield. After four years sourcing advertising, overseeing the production and distribution, as well as being a regular contributor, Fiona is moving on to new business ventures.

The Editorial Board and Council of the Institute wish her well and thank her for her tremendous efforts in making the *Journal* the vibrant and interesting read it is today. The next issue welcomes Anthea Lees as she steps into this position.

NEWS

Congratulations to Dr *Penny* ***Brothers*** (Auckland University) who was appointed ***Professor*** as we went to Press.

QUEEN'S BIRTHDAY HONOURS

Council congratulates Emeritus Professor *George* ***Clark*** on his appointment as an Officer of the New Zealand Order of Merit (OMZM). Physicist and materials scientist *Jeff* ***Tallon*** (IRL and VUW) was appointed a Commander of the Order.

NZIC MEMBERSHIP MATTERS

We welcome to the Institute the following new members:

MNZIC

Auckland University:
Dr Jonathan Sperry

Otago University:
Dr Stephen Moratti

IRL Wellington:
Drs Owen Catchpole, Alistair Ian Longshaw, David Clarke and Benjamin Compton

Thermal Chemistry Ltd, Waikato: David Richard Addison

Student Members:

Auckland University:
Sumit Lal

Canterbury:

University:
Sandra Atkinson, Robert Currie, Rachel Hanover-O'Connor, Lauren Pinfold, Captain M J Rushworth, and Mark Russell

CPIT:
David Ashton, Leonard Hettige Don, Chandan Pal, and Anthony Strachan

Massey University:
Janice Moody

Otago University:
Matthew Smart and Emily Lei Wang

Victoria University:
Peter Clark, Ashna Khan, Ben McCartney, Peter Moore, and Melanie Nelson

BRANCH NEWS

AUCKLAND

Auckland University - Chemistry

Chemistry HoD Prof *Jim* ***Metson*** spent six weeks during April-May in Norway on research leave. He attended the 1st Iranian International Aluminium Conference in Tehran, and then spent time at the Hydro Research Centre in the Herøya Industry Park, containing a major fertilizer plant, a Si facility for solar cell fabrication, and the old site of the Hydro Magnesium Plant. OSH regulations required Jim to wear a hard hat and carry a gas mask simply to move between buildings – not yet required on the Auckland campus!

The May Science graduation included a morning tea in the Department where acting HOD A/Prof *Penny* ***Brothers*** announced that *Tanya* ***Grkovic*** was the winner of the L.H. Briggs Medal for the best 2008 Departmental PhD thesis. Tanya is expected to graduate at an October ceremony. Amongst the graduates was Chemistry Department Manager *Cathy* ***Comber*** who received a PGDipBus (HRM).

Zoe ***Wilson***, a PhD student with Prof *Margaret* ***Brimble***, was one of 200 students worldwide selected to attend the prestigious 39th St. Gallen Symposium in Switzerland, in May. Zoe's winning essay, *Can a researcher be an island*?, highlighted the importance of collaboration between scientists.

Prof *Graham* ***Bowmaker***'s retirement was marked with a function at Old Government House in early April, which was attended by a number of former staff members. Graham will continue to be a valuable presence within the Department alongside some well deserved retirement activities. Dr *Vitorrio* ***Caprio*** left the Department in April to take up a post back in Wales.

Recent Departmental seminars have included Dr *Ali* ***Hosseini*** (Standford University, and a former Auckland PhD student) on *Interdigitated array microelectrodes*; Prof *Digby* ***Macdonald*** (Penn State University and an Auckland graduate) on the *Limits of Passivity and Our Metals-Based Civilization*; Prof *Michael* ***Fryzuk*** (University of British Columbia) on *Activation and Functionalization of Molecular Nitrogen by Transition Metal Complexes*; Prof *Richard* ***Jackson***, (Sheffield University) on *Amino Acid-Derived Organometallics: Applications and Solution Structure*; Prof. *Ted* ***Baker*** (Auckland) on *Discovery through Crystallography*; Dr. *Mario* ***Blanco*** (Beckman Institute, CIT, Pasadena) gave a seminar on the *The Future of Nanosensing*.

The Department had funding successes in the form of a FRST TRST *Materials Accelerator* programme ($NZ 2.4 M p.a. for 4 years) from a bid led by Prof *Ralph* ***Cooney*** with participation of several staff. Prof *Margaret* ***Brimble*** was awarded $US 750,000 for 3 years from the US Human Frontiers Science Grant on Antifreeze Proteins in Fish jointly with A/Prof *Clive* ***Evans*** (Biological Sciences) and American collaborators.

CANTERBURY

The April and May events have been dominated by researchers associated with the University of Cambridge, either as current or as previous members of staff. In April, Professor *Alison* ***Smith*** (Plant Science) delivered an excellent talk on *Vitamins-R-Us. What are Vitamins and Who Needs Them?* to a large and enthusiastic audience. On May 27th the Branch was privileged to have not one, but two fascinating talks on topical issues over drinks and nibbles. Dr *Rob* ***Somekh***'s talk on *Sustainablity without the Hot Air* and Dr *David* ***Jefferson***'s talk on *Nanoparticles: Crystalline or Molecular?* were well received by a good turn out of NZIC members.

CPIT

Congratulations to School of Applied Science and Allied Health students who graduated in March. *Heather* ***Raynor***, *Leanah* ***Magon***, *David* ***Ashton*** and *Robyn* ***Dawrant*** received the BAppSci (AUT), *Yi* ***Chen*** and *Anthony* ***Strachan*** were awarded the Diploma in Science (Level 6), and *Margarita* ***Koshchienko*** and *Iulia* ***Pescariu*** gained Graduate Diplomas in Laboratory Technology. NZIC-sponsored prizes were awarded to the top analytical chemistry CPIT students in 2008. *Leonard* ***Hettige Don*** was the best student in Analytical Chemistry 5, *Chandan* ***Pal*** best in Bio-analytical Chemistry 6, and *David* ***Ashton*** best in Analytical Chemistry 7.

In May, 24 teams from 14 schools around Christchurch took part in CPIT's Year 12 Chemistry Competition. Each team of three students had one hour to carry out a range of chemical tests to identify a number of unknown organic solids and liquids. Following the competition, the students enjoyed a light supper, courtesy of NZIC sponsorship. The winning team was from Riccarton High, with second and third places going to Cashmere High and Kaiapoi High Schools, respectively. The Year 11 Chemistry Competition will be held at CPIT on Thursday the 24th of September.

University of Canterbury

Congratulations to students who have recently completed MSc and PhD degrees: *Jeni* ***Burgess*** (PhD) with her thesis on *Aspects of Metallosupramolecular Chemistry* (supervised by *Peter* ***Steel***); *Lin (Jackson)* ***Sun*** (PhD) on *Applications of New Technologies for the Rapid Identification of Compounds from Natural Sources* (Profs *Murray* ***Munro*** and *John* ***Blunt***, and A/Prof *Tony* ***Cole*** in Biology); *Paul* ***Thornley*** completed his MSc on *The Synthesis and Characterisation of a Novel Polyamine-Terpyridine Ligand and Related Complexes* (*Richard* ***Hartshorn***).

Congratulations to *Philipp* ***Emnet*** on receiving the Christchurch City Council Antarctic Scholarship, which will allow him to travel to Antarctica for one month in the coming season to carry out field work as part of his PhD examining the analysis of emerging endocrine disrupting compounds in NZ and Antarctic ecosystems.

Recent visitors to the Chemistry Department have included Dr *Dónal* ***Leech*** (School of Chemistry, National University of Ireland, Galway) who has interests that include chemical attachment of redox complexes and enzymes to electrode surfaces. Prof *Jeff* ***Keillor*** (Université de Montréal) is the latest Erskine Fellow. His research interests include enzyme mechanisms, inhibition and engineering, and the development of new protein labelling technologies. Prof *David* ***Jefferson*** is the Department's first Cambridge/Canterbury Fellow. His research interests include electron diffraction, electron microscopy and nanoparticles.

Dr *Jan* ***Wikaira*** is on sabbatical until August at Clark University (Worcester, Mass.) working with Prof. *Mark* ***Turnbull***. Dr *Quentin* ***McDonald***'s Adjunct Senior Fellowship has been extended until 31 March 2012. Quentin is an expert in computational chemistry and his company, Q-Bit(NZ), is NZ's sole producer of molecular modelling software and (amongst other things) is contracted to Schrodinger to develop the program Maestro. Over the past three years Quentin has collaborated with Prof *Jim* ***Coxon*** and A/Prof *Emily* ***Parker***.

MANAWATU

The annual NZIC student BBQ was a blast – literally! The BBQ was being well tended and supervised by one *Adrian* ***Jull***. One event led to the next, which ended with the fire alarm being triggered and the fire department making a lively house call to check that our NZIC BBQ meat wasn't being overcooked to a crisp. Otherwise the evening went without further mishap and everyone enjoyed the scrumptious food and beverages provided. A student poster session was held during the event with first prize going to *Hillary* ***Corkran*** and *Serena* ***Smalley*** second.

Once again, a combined Postgraduate Research Symposium was held covering presentations from postgraduates in all four disciplines of IFS. There was a great turnout of staff and students and the event concluded with a Happy Hour at Warerata where prizes were awarded; *Aurelie* ***Cucheval*** won the best presentation from the Chem/Physics students.

In April, Dr. *Vladimir* ***Havlicek*** (Institute of Microbiology, Academy of Sciences, Prague) gave a talk on the use of mass spectrometry in the biosciences and *Troels* ***Jensen*** (a visiting PhD student from the University of Southern Denmark) spoke about his research area in *Unlocked Nucleic Acids)*. The 15th saw Dr *Jóhannes* ***Reynisson*** (Chemistry & Bioengineering, Auckland) discuss computer aided drug design and DNA damage, while at the end of the month, Prof *Keith* ***Gordon*** (Otago), addressed us on *Designing New Molecular Electronic Materials: Strategies from Density Functional Theory and Spectroscopy*. May 12 saw the first of the NZIC Presidential addresses. Prof *John* ***Spencer*** (VUW) gave his *Hydrogen – the Cinderella of Chemistry* presentation. The end of May had Prof *Stephen* ***Henderson*** (Materials Sciences and Nuclear Engineering, University of Maryland, USA) speak about small-angle X-ray and neutron scattering for solution studies.

In early April A/Prof *Trevor* ***Kitson*** was presented with his RSNZ Medal for Science and Technology and for his leadership in chemical education and on May 1 Prof *Andrew* ***Brodie*** officially retired from Massey University. However, he still has many research commitments to complete before he contemplates departing the campus. To this end, he has been honoured with the title of Emeritus Professor, which means we will still be seeing him roaming the corridors of the Institute for some years yet. Many of Andrew's peers, colleagues and friends attended the farewell, and in typical IFS/IMBS fashion, a troupe of performers gave a couple of splendid renditions of *Yesterday*.

Medhat ***Al-Ghobashy*** has submitted his PhD thesis *Downstream Purification and Analysis of the Recombinant Human Myelin Basic Protein Produced in the Milk of Transgenic Cows. Quintin* ***Knapp*** has completed his MSc in Chemistry (1st Class) while *Janice* ***Moody***, a BSc (Hons) chemistry student, has won a Graduate Women Manawatu Postgraduate Scholarship. *Emad* ***Al-Imarah*** and *Indu* ***Sharma*** (A/Prof *Ashton* ***Partridge***) and *Olekile* ***Tibe*** (A/Prof *David* ***Harding***) have commenced PhD study in Chemistry.

Dr. *Jeraime* ***Griffith*** began a two year postdoctoral appointment in early April with *Vyacheslav* ***Filichev*** and *Gareth* ***Rowlands*** on a project entitled *DNA: a new code for catalysis*. He will seek answers to fundamental questions about the ability of DNA to induce selectivity in organic reactions, thereby opening up new vistas in asymmetric catalysis, ultimately enabling the development of a new type of catalyst. The project is at the interface of chemical biology and organic chemistry, yet at the cutting edge of both.

Rachel ***White*** and *Tracey* ***McLean*** have both been awarded $1000 from the RSNZ travel fund to attend the 21st American Peptide Symposium *Breaking Away* (Indiana University) and the 18th International Symposium on the Photochemistry and Photophysics of Coordination Compounds, in Hokkaido, Japan, respectively.

The Australian Synchrotron

At the end of April Prof *Geoff* ***Jameson*** travelled to Melbourne to join collaborators at the Australian Synchrotron. They were beta users of the new protein crystallography beam-line, PX2, commissioned by Dr *Tom* ***Caradoc-Davies*** (Otago – and an occasional user of the protein X-ray facility at Massey). The PX2 beam-line is optimised for microcrystals, not only of proteins and macromolecules but also of smaller molecules. Crystals only a few of microns in maximum dimension size can be used, but the intensity is so high that it is a race to gather data before the crystal is fried. If you get the chance to visit the synchrotron, either as a tourist (or better yet as a scientist) go. About 20 students from NZ are heading to Melbourne in July for the First Australian Synchrotron Winter School, covering IR, SAXS, powder diffraction, X-ray absorption spectroscopies and protein crystallography. Immediately after this workshop, the NZ Synchrotron Group is running a separate specialist protein and small-molecule workshop on PX1 and PX2 beam-lines. It is hoped this becomes an annual event. And it's free!

OTAGO

The Annual Branch Dinner was held at the Mellor Restaurant on May 20. Em Prof *David* ***Jones*** (Microbiology & Immunology, Otago) entertained the audience during the after-dinner lecture with stories about his lifelong interests and adventures in biofuels and biobutanol. Activities planned for the year include visits to Emerson's Brewery and the Macraes Gold Mine.

Otago University - Chemistry

After 12 years at the University of Otago, *Henrik* ***Kjaergaard*** has accepted a position as Professor of Physical Chemistry at the University of Copenhagen commencing in August. While at Otago, Henrik supervised 10 PhD and 20 Honours students and has made many contributions to teaching, research, and service that are well-recognized within the University.

Lindon ***Moodie*** (PhD student, Larsen group) was awarded the Branch-sponsored NZIC Communicator Award for his poster at the NZIC Conference last December (unfortunately this was omitted from the April News). *David* ***Warren*** has been awarded a RSC Travel Grant to present a paper at the IUPAC Congres in Glasgow in August. *Ruma* ***Ghosh*** (PhD student, Hageman group) was awarded the 2009 Kelly Tarlton Antarctic Postgraduate Scholarship; she accepted her award and presented a poster at the Antarctic Conference in Auckland in July.

Jim ***Simpson*** recently spent two weeks as a Visiting Professor at the Universiti Kebangsaan Malaysia (UKM) in Bangi, Malaysia. In addition to reviewing their Chemical Technology course and giving lectures, he also ran a very successful workshop on publishing crystallographic data for staff and students of UKM and several neighbouring universities. A welcome attendee at this workshop was *Ward* ***Robinson***, recently retired from the University of Canterbury. Ward has been a Visiting Professor at the University of Malaya for more than a year, teaching their postgraduate students to use the diffractometer and solve structures.

Brookers Bunch has welcomed new postdoctoral *Holger* ***Willms***, fresh from completing his PhD at Dusseldorf University. *Jonathan* ***Kitchen*** is congratulated on gaining his PhD with his thesis on the Division of Sciences List of Exceptional PhD theses. Jonathan and *Matthew* ***Cowan*** (BSc Hons. 1st) graduated at the May ceremony with *Humphrey* ***Feltham*** (MSc with distinction, 2008), graduating *in absentia*. Matthew and Humphrey are presently PhD students and Jonathan is a postdoctoral in Brookers Bunch. *Jonathan* ***Sessler*** (University of Texas) visited in April as a William Evans Fellow and gave a lively and well-received 400-lecture course on *Supramolecular Chemistry*, which was also attended by many postgraduates and some staff. Sally Brooker left for Europe in mid-June to present invited lectures at the ISMSC conference in Maastricht and the Supramolecular meeting in Dublin. She will also participate in the RSC CCDG meeting in Leeds, and visit a number of collaborators in Germany, Switzerland and Ireland.

Keith ***Hunter*** (Marine and Freshwater Chemistry Group) was interviewed about ocean acidification and its potential effects on the NZ shellfish industry by National Radio in May. The group also hosted a camera crew from Rural Delivery (TV1), who prepared a segment on the same topic, which was broadcast in early June. Honours student, *Allanah* ***Paul***, travelled to Wellington to accept a Freemasons University Scholarship, presented by Prime Minister, John Key. These scholarships are awarded to A students who are also involved in non-academic community activities. PhD student, *Melanie* ***Gault-Ringold*** was awarded a Travel Grant from Vincent George House of Travel after giving an excellent presentation *Cadmium Isotopic Compositions and Nutrient Cycling in the Southern Ocean*. This award will allow her to present her results at the Goldschmidt 2009 Conference in Davos, Switzerland.

The outreach group has been very busy visiting local intermediate schools and designing chemistry modules that have proved very popular with students and teachers. These activities are in response to requests from local schools for help in increasing/improving the science content that Year 8 students receive. It is part of the long-term outreach strategy the Department is developing to support local schools. On 30 April, after a nervous trip in a chemical-laden van driving up State Highway 1, *Daniel* ***Hutchinson***, *Richard* ***Souness***, *Jacqui* ***Kao,*** and *Katie* ***Wilson*** inflicted collective mayhem on Year 13 chemistry classes at Waitaki Boys and Waitaki Girls High Schools. During the visit, onions were frozen, hydrogen balloons exploded, stalagmites made, and a toilet window broken by a (very cold) flying banana. Daniel also gave a lucid explanation of the chemiluminescence of luminol in the presence of copper(II) ions and Richard tortured a jelly baby called Henry. Overall, it was an enjoyable day for all and the group has been invited back to perform to Year 12 students later in the year. A slightly more serious side came when project students (Phillippa Sutton) delivered the lesson she had developed on acids and bases to the Year-10 classes.

Jacqui Kao freezing an onion in liquid nitrogen - part of the Otago University Outreach visit to Waitaki Girls High.

WAIKATO

Earlier this year the Waikato NZIC Branch held their annual student recruitment barbeque, which had a great turn out and hopefully will encourage some new students to join up. More recently, we have had a talk by *Colin* ***Milne***, a recipient of a Royal Society of New Zealand Science, Mathematics and Technology Teacher fellowship, who spoke on work he had done during this felllowship and challenged our perceptions on the nature of science. He also introduced us to the website *www.sciencelearn.org.nz* which provides resources for teaching science.

University of Waikato

As previously announced, *Derek* ***Smith*** retired from the Chemistry Department after 36 years. Derek obtained his BSc (Hons.) degree at St Andrews, then a DPhil at Oxford working with R. J. P. Williams. He then was a postdoctoral fellow/assistant lecturer at the University of Sheffield before being appointed to Waikato in February 1973. Derek was the eighth member of the Department (and the second inorganic chemist with *Ken* ***Mackay***) preceding *Brian* ***Nicholson*** and *Alistair* ***Wilkins*** in 1975. In 1980, Derek was a finalist on the NZ TV show *Mastermind* and was well ahead in his specialist topic but was beaten on general knowledge by some tough questions. Specialist topics in final and earlier rounds were centred on British Battleships of the Late 19th Century and World War I. His success helped raise the profile of the University in its earlier years.

Derek was also the subject of a spoof complaint to the Waikato student magazine *Nexus* probably in the late '70's, from 3rd year Chemistry students expressing shock at the apparently lascivious nature of an original mnemonic for the lanthanide elements in the periodic table. The mnemonic itself was not published but it was widely recognised as behind a surge in the numbers of students clamouring to take inorganic chemistry the following year.

As a theoretician, Derek has been interested in bonding models and the fundamental understanding and use of concepts such as electronegativity, and he has applied these to problems ranging from transition metal complexes (especially those of copper) to pure organic compounds. He has always been concerned with teaching these ideas to undergraduates and many of his articles have been published in *J. Chem. Ed*., illustrating nicely the philosophy propagated by universities that teaching should be informed by research activities. In addition to writing original research articles, Derek has been the reporter for the copper chapter of the *RSC Annual Reports on Inorganic Chemistry* for more than 10 years, and was invited to contribute the section on bonding in transition metal complexes for the *Encyclopaedia of Inorganic Chemistry*.

In addition to the University's recognition of Derek's retirement, Derek hosted a very well attended function for his many colleagues and friends at which time he performed his famous rendition of the poem *The Tay Bridge Disaster* by William McGonagall. He is acclaimed as the worst poet in British history so, not to be outdone, Ken Mackay recited the very clever poem below that he had written especially for the occasion.

Derek's Retirement

Derek completed the second cohort [organic, physical, analytical and inorganic] in Waikato's build-up in the early 1970's. His DPhil was from Oxford – *the other place* – so it was a case of:

Fair fa' your honest sonsie face
New chemist from the other place
Amang them a' you tak your place
Alan, - Lyndsay, - Chris

Things do not get better than this

He gave us the ideas Of Williams, R. J. P.
On metals in bio-chemis-tree
And wave functions both plus and minus
In the schemes - of Pauling, Linus
As for the mnemonics for each Lanthanide element
On those I couldn't possibly comment

But then we come to the real show-stopper
The absolutely entire chemistry of copper
Biological beasts – co-enzyme XYZ
He had all the details in his head
Complex oxide species and warm superconductors
In these he delighted to instruct us

Interlude

New Agers might wield
Their Crystal Field
And claim that compounds were yeller
He shewed it was true
That each one was blue
By application of Jahn-Teller

Resume

Numbers and data were Derek's delight
He could think of them all day and all night
Ionisation Potentials and Electron Aff-in-ities
Giving rise to strange E-lectro-neg-a-tivities
Advocating ideas, really quite heretical
He is the very model of a chemist theo-retical.
Bond lengths and bond angles, shapes and symmetries
He rejoiced in such things as these
In deep consideration of structures un-symmetrical
He is the very model of a chemist theo-retical.
Some he wrote up, in Latin patter
And published in Theo-retica Chimica Acta.
Derek rejoiced in data of every kind
As discovered by viewers of Master-mind
The whole country learned, he knew de-tails galore
Of battleships and the First World War
And still they gazed, and still the wonder grew
That one small head could carry all he knew.

But now the Time Has Come, he moves side of stage
Lets Brian and Bill the battles wage
Enters the Third --- The Golden Age
Perhaps in contemplation turns
To African Violets and the works of Burns
But instead he may Write-it-all
Then, oh Help, Recite-it-all
In the style of that distinguished and no-ble poet, - popular in his own lifetime,- and later strangely neglected -but in more recent days experiencing a revival - thanks in no small part to the publish-ing interests of Derek's father Where was I? Ah yes
Write-it-all Recite-it-all
In the style of MAC GON A GALL
So join with me, one and all
In wishing Mandy and Derek a long, prosperous and interesting retirement.

MSc student *Benjamin* ***Deadman*** was recently selected to attend the 59th Meeting of Nobel Laureates in Lindau (Germany) in early July. Nominated by RSNZ, he joined 600 other young researchers from more than 60 countries, in a week of lectures and group discussions with about 20 Nobel Laureates. PhD student *Jonathan* ***Puddick*** and MSc student *John* ***McDonald-Wharry*** presented posters at the NZBio conference *Bio Solutions for a Changing World* in Auckland last March. Again, the conference showcased the commercialisation of science and innovative new technologies. Jonathan's poster, describing eight new microcystins from an Antarctic cyanobacterium, gained 3rd place in the poster competition. Along with fellow students *Nicky* ***Cameron*** and *Ashleigh* ***Richards***, he also presented his poster at the student biotechnology event hosted by the Waikato Branch of NZBio.

On his annual visit to the Department Prof *Neil* ***Ward*** (Surrey) gave a very interesting talk *Arsenic - the Silent Killer?*, which outlined the global problems of arsenic and associated chemicals in ground waters and soils, and the methods of measuring arsenic speciation and possible remediation technologies.

WELLINGTON

The March meeting of the Branch saw an address by *Tim* ***Couttes*** of the National Renewable Energy Laboratory of the US in Colorado as we recorded previously. In April, Dr *Andy* ***Kay*** of IRL described his Photonics Group research on zwitterionic chromophores for nonlinear optical (NLO) devices. He gave our members a good introduction to NLO materials, the essential criteria that these must meet in order to have any possible industrial significance, and the work the group has done with a range of π-extended donor-acceptor chromophores. The 2009 Presidential Address was delivered by Prof *John* ***Spencer*** on May 13 entitled. *Hydrogen – the Cinderella of Chemistry?* John drew the largest audience of any recent NZIC meeting with in excess of 50 keen attendees who were not disappointed by his survey of the hydrogen usage and its role in his own research. By the time this is in print John will have visited a number of Branches.

Victoria University

Recent visitors have included Dr *Maria* ***Matvenko***, a former student who has gained her PhD from ANU (*Martin* ***Banwell***), who spoke on her work involving the chemenzymatic syntheses of various natural products. She has been working in the carbohydrates group at IRL over recent months and is about to take up a Humboldt postdoctoral fellowship in Munich. Prof *Mike* ***Fryzuk*** (University of British Columbia) gave a seminar in late March on the *Activation and functionalization of molecular nitrogen complexes* spending much of his time in the School with the Spencer group. Early April saw Prof *R.F.W.* ***Jackson*** (Sheffield University) speak on *Amino Acid-derived organometallics; applications and solution structure*. His work emphasizes the use of organozinc chemistry in the synthesis of unnatural amino acids. At about the same time Prof *Bradley* ***Williams*** (Johannesburg University) broke his NZ vacation to visit the School and tell us about his *metal triflate-promoted organic syntheses*. Apart from providing us with some elegantly simple chemistry he showed the great virtue of following up on work and gleaning financial support from industry.

Dr. *Winai* ***Somboon*** (Kink Mongkut's University, Bangkok) visited VUW in May and his day in SPCS featured a lecture on *Waste Utilization and Pollution Control* in which he outlined the successes his group has had in minimizing pollution in small-scale Thai industries. Although the levels of local pollution permitted exceed NZ's norms, the improvements that he has introduced are more than significant in the local scene.

With Dr *Brendan* ***Burkett***'s departure to Singapore last December, *Joanne* ***Harvey*** on maternity leave until July, Prof *Brian* ***Halton*** was brought out of retirement to attend to some 300-level teaching. However, Dr *Rob* ***Keyzers*** has now arrived taking up the fourth organic position.

Article

Witches, Horses and Dead Turkeys

Denis R. Lauren

The New Zealand Institute for Plant and Food Research Limited, Ruakura, Private Bag 3123, Waikato Mail Centre, Hamilton 3240 (e-mail: *dlauren@hortresearch.co.nz*)

The Common Link

St Anthony's Fire and Salem witches, what do they have in common with the food-related deaths of about 10% of the Siberian population during World War II, or the death of 100,000 turkey poults in England in 1960? Do they have anything in common with the death of horses and farm workers in Russia in the late 1930s and 40s, with the sudden death of infants in poor districts of Cleveland (Ohio) in the 1990s, or the high incidence of oesophageal cancer in humans in south-western Transkei, and in Linxian County of Henan Province in China? And where do photosensitised or barren sheep on NZ farms fit into the picture? The answer is fungi – fungal infection of food or other materials, with resultant contamination by mycotoxins.

Despite such sporadically acute and locally devastating events, and other less spectacular chronic mycotoxin-induced diseases in humans and animals, mycotoxicoses remain mainly *neglected diseases*. While some people see the hand of mycotoxins in the Plague of Athens that broke out *ca*. 431 BC during the Peloponnesian war, or in the biblical account of the ten plagues of Egypt,[1] others see the topic of mycotoxin contamination as a ploy by some researchers to keep their jobs. Still others see it as an unnecessary imposition by bureaucrats intent on setting food or tariff barriers, while more again see it as a complex and many-faceted subject they know is important, but do not know how important. It is the complexity that makes the topic both interesting to adherents, and suspect to those who find it all too much.

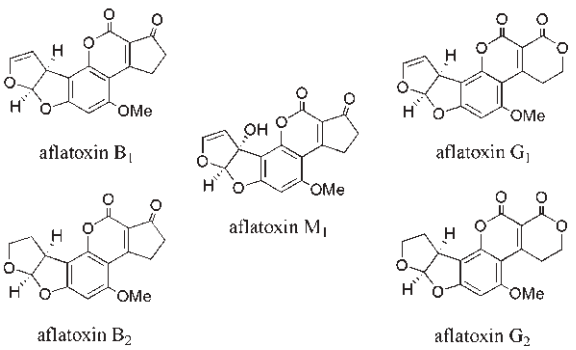
Mycotoxins – What are They? Where do They Occur?

Mycotoxins are toxic secondary metabolites produced by fungi. They come in many and varied chemical structural types. The toxicity tag is related to humans and other animals and so does not include other fungal metabolites that might be insecticidal or herbicidal. Some mycotoxins could be all of these.

Many different genera of fungi produce mycotoxins, and within each genus there are commonly both toxigenic species and non-toxigenic species. Even within a normally toxigenic species there can be isolates with widely differing ability to produce toxins, and also, quite different environmental parameters within which each isolate best produces those toxins. To add further to the complexity, while a specific toxigenic species will generally produce a predictable toxin class, there is a varying ability to produce other related toxic metabolites, occasionally including the ability to produce a toxin class generally associated with another species from the same genus.

Mycotoxins can occur in many food crops including grain, nuts, herbs and spices, fruit, vegetables, dairy products, and in many processed foods made from these.[2,3] The most widely recognised mycotoxin class worldwide is that of the aflatoxins, B1, B2, G1 and G2,[4] and their mammalian metabolite found in milk, M1[5] (Chart 1). The aflatoxins were first isolated and identified in relation to the turkey poult deaths in the 1960s.[4] The cause was traced to Brazilian peanut meal, and this shows a particular aspect of the risk from mycotoxins such as the aflatoxins. Since they can occur in a number of the major human food or animal feed commodities traded worldwide (maize, nuts, spices, dried fruits, copra), they represent a constant international issue for these commodities and for products made from them.

Chart 1. Aflatoxins



Aflatoxins are not a risk in NZ-grown produce, but they can be found in imported products and, therefore, are a potential risk to human and animal health and, should dairy animals be fed contaminated materials, in the contamination of milk. This exemplifies one of the traps of mycotoxin discussions. Mycotoxin production (which toxins and how much of them) is highly specific to each environment and depends on the specific substrate and environmental conditions existing at the time. Thus, generalized discussions based on general international data may have overview informative value, but cannot predict the local risk. One must understand the risk factors and their causative factors in order to understand the probability of a particular product being contaminated.

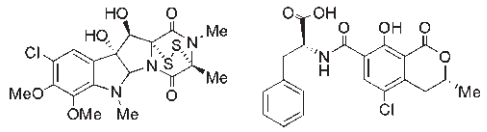
In essence, there will be distinct issues with locally grown products and with imported products. There will be a *local risk* generated by local fungal species interacting with the local environment, and an *imported risk* from products imported from different countries, each with their own range of fungal species and causative environmental factors. The temptation to leap on the current international bandwagon and analyze for the latest buzz contaminant should be avoided, unless there is good reason to suspect a real risk from that contaminant. As this article will demonstrate, the *real risk* can be assessed through a combination of mycological and chemical knowledge and experimentation.

The New Zealand Scene

Perhaps the best known mycotoxin problem in NZ is facial eczema, a seasonal syndrome caused by the toxin, sporidesmin (Chart 2), which is produced in the spores of the fungi *Pithomyces chartarum*.[6] The syndrome is expressed in animals feeding on very short grass and dry plant litter where rain and high humidity follow periods of drought. Two other mycotoxins that represent actual or potential regulatory risks for NZ products are ochratoxin A in wine (from *Penicillium* infecting fruit)[7] and patulin (both in Chart 2) in apple juice (also from *Penicillium*, albeit other species, infecting fruit).[3] These will not be covered here.

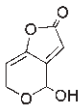
This article focuses on mycotoxins in grains, especially those produced in NZ. As an example of how to track and verify a true mycotoxin risk, investigations undertaken by the author and colleagues of the impact of *Fusarium* species and their mycotoxins in NZ grain (especially), and pasture will be outlined.

Chart 2. Miscellaneous mycotoxins

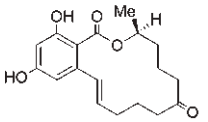


sporidesmin A

ochratoxin A



patulin



zearalenone

Initial Work on Fusaria in NZ

Before our work began in the early 1980s, very little was known about the impact in NZ of *Fusarium* species and their mycotoxins. This species had come to prominence a few years earlier through intensive study in North America into crop diseases such as Fusarium head blight in wheat and Fusarium ear rot in maize.[8] There was also a claim that *Fusarium* mycotoxins had been used as chemical weapons against local populations in Laos in the form of *yellow rain*.[9]

Our involvement came as part of a group studying the cause of surprisingly poor fertility in sheep grazing dry land in the Gisborne region; these animals were otherwise doing well. Investigation showed that the pastures contained a high incidence of several *Fusarium* species, some of which had been reported to produce the estrogenic mycotoxin, zearalenone (ZEN) (Chart 2).[10] Samples of the dry pasture litter revealed the presence of some moderate levels of ZEN,[11,12] and subsequent animal studies showed that doses of this toxin, at about the same daily intake levels expected from the pasture contamination levels, could, indeed, produce the reductions in fertility seen in the field.[13] Studies to provide a full understanding of the impact of this toxin on pasture-grazing animals were pursued by researchers in AgResearch, while we (in HortResearch at that time) focused mostly on the impact of *Fusarium* fungi and mycotoxins on NZ-produced cereal crops.

NZ grain crops

This work commenced in 1985 when little was known about the mycotoxin status of NZ-produced grain. Research and farming aims were focused primarily on the production of higher yields and higher profits, achieved by advances in cultivars and hybrids and agronomic practices. Some consumer groups such as pig farmers were finding sudden unexpected problems in their systems, with some loss of animals and poor growth rates in survivors. Maize, as a feed component, became suspect.

With the then internationally high research interest in mycotoxins in foods and feedstuffs, it was tempting to purchase some standards of the current main interest mycotoxins (aflatoxins, trichothecenes, fumonisins) and start analysing NZ products for them. We did report[14] on the occurrence of *Fusarium* mycotoxins in NZ wheat in 1986 and, subsequently, other researchers reported on their occurrence in maize.[15] However, rather than initiating widespread unguided screening of crops, we decided instead to apply our pasture/zearalenone experience and determine firstly, which toxigenic fungal species most commonly occurred in NZ-produced grain, and then, using culture experiments, the toxins that they could produce.

Links with the research group of Agriculture Canada led by Roy Greenhalgh and David Miller led to limited examples of NZ *Fusarium* species being taken to Canada in 1985 and assessed for their ability to produce mycotoxins in culture. This work showed that NZ species did produce known mycotoxins, or at least the *in vitro* modified derivatives of them.[16] In the course of these studies, several interesting new fungal metabolites from early in the biosynthetic pathway were isolated and identified.[17] This early study not only provided some novel and instructive chemistry, but also gave an insight into the behaviour, in culture, of the NZ fungal isolates. Subsequently, a thorough investigation of *Fusarium* fungal species infecting different cereal crops grown as commercial or trial plots in the different regions of NZ was undertaken. This was done by collecting samples of maize, wheat, barley, and oats at harvest from multiple crops from Auckland to Southland.

All these samples were subjected to intensive mycological investigation to determine which *Fusarium* and other species had infected them.[18] This showed which ones could have potentially produced mycotoxins had conditions been favourable. At about the same time, further collections of *Fusarium* species were made from autumn pastures to see how these related to the species found in the grain crops. Rather than simply relying on literature data from the identified fungal species to dictate which mycotoxins would be expected in the grain crops, examples of all species isolated were grown in culture and then examined for production of known toxic metabolites.[16,19] This approach yielded some unusual findings, and also provided a solid guide to exactly which mycotoxins were the most likely to be found as contaminants of NZ-grown grain crops. Subsequent analysis of all the harvested grain samples showed the actual mycotoxin contamination to be as expected from the fungi isolated from that grain and

the mycotoxin-producing potential that the isolated fungi revealed in culture.[20]

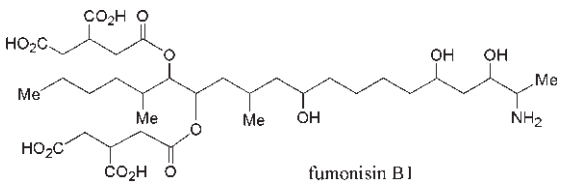
Fusarium Species Most Commonly Found in NZ Grain and Pasture

Table 1 shows the six most commonly found *Fusarium* species in grain and pasture grown in NZ. The dominant species and their relative percentages found depended on crop, region, and year. Of the recognised toxigenic species isolated, the dominant ones were *F. graminearum*, *F. crookwellense*, and *F. culmorum*.[12,18] All these are known to produce examples of the trichothecene class of mycotoxins, and also ZEN – consistent with the early findings of ZEN in problem pastures. Other common species isolated are considered to produce mycotoxins less frequently in real life situations.

Table 1. Common Fusarium species found in different crops grown in NZ.

***Fusarium* spp.**	***Overall mean % in crop***				
	Maize	Wheat	Barley	Oats	Pasture
F. avenaceum	-	22	22	30	15
F. crookwellense	24	4	5	1	29
F. culmorum	2	25	14	15	15
F. graminearum	52	30	22	4	2
F. poae	7	14	23	43	-
F. subglutinans	13	-	-	-	10

A common mycotoxin risk to maize worldwide is from the fumonisins, *e.g.* B1 produced by *F. verticillioides* (formerly *F. moniliforme*). However, the incidence of this species in NZ-grown maize is very low, and typically ‹‹1% of all fungi isolated from maize kernels. Accordingly, any proposal to screen NZ maize extensively for fumonisins would yield little of value, even though low levels of fumonisin have been reported in grass samples from an Otago pasture.[21] Thus, it is not surprising that NZ grown maize is situated among the lowest risk from fumonisins worldwide, albeit from limited testing. It will be interesting to see whether the effects of global warming change this for northern parts of NZ. The first clue will be an increase in the incidence of *F. verticillioides* in the maize.



fumonisin B1

Investigation of Toxigenic Potential in Culture Experiments

By examining the toxic metabolites produced by local pathogenic fungal isolates in culture, one can gain a direct guide to those toxins that, potentially, would be found in the host food crops if mycotoxins were produced in the field. This approach provides a better lead to which contaminants (including uncommon ones) to screen local crops for by chemical analysis. The alternative approach of relying on international literature and simply purchasing a (necessarily limited) selection of commercially available chemical standards for screening is less reliable and may result in some locally-important contaminants being overlooked.

A common way to culture fungi in order to determine their toxigenic potential is by use of solid culture media such as rice or corn. Such media can produce a useful array of toxic metabolite variations, but have the disadvantage of producing complex extract mixtures carrying many co-extractives that must be removed prior to isolating the compounds of interest. An alternative uses defined liquid culture media and it provides much cleaner extracts, although it is limited in that not all potential toxin classes may be expressed in liquid culture, *e.g.* ZEN production is favoured in solid media whereas it is virtually eliminated in liquid media.

To study factors driving ZEN production, solid media experiments are necessary. Using solid media, isolates of *F. crookwellense* and *F. culmorum* that produced ZEN and multiple related metabolites (such as the α- and β-zearalenols and zearalanols) were determined,[16] as were other isolates of *F. crookwellense* that produced ZEN almost exclusively. One of the latter group of isolates produced as much as 20 g of ZEN per kg of maize media under ideal conditions.[22]

Trichothecene production, on the other hand, while good in solid culture, is also very well expressed in liquid culture and this is preferred. A variation in liquid culture is that trichothecenes tend to be expressed as acetylated derivatives rather than the deacetylated versions from solid culture and in harvested grain. This approach is still suitable to study toxigenic capability and overall risk, however.

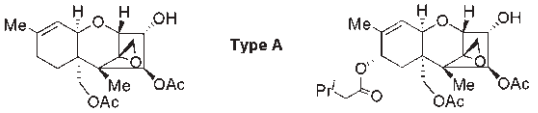
Trichothecene Mycotoxins Produced by Fusarium Species Isolated in NZ

The trichothecenes are a group of sesquiterpenes that occur in four structural variations, each representing either the Type A or Type B variant (Chart 3). Interest in them developed following the severe mycotoxicoses events in Russia in the 1930s, 40s and 50s. T-2 toxin (Chart 3), in particular, was implicated in those outbreaks and is one of the more toxic trichothecenes.[23]

Of *Fusarium* species commonly found in NZ-produced grain, *F. graminearum* was, and still is, widely reported internationally as a producer of deoxynivalenol (DON) (Chart 3), with different chemotypes producing, in culture, either 3-acetyl-DON or 15-acetyl-DON as the preferred acetylated derivative. In 1983, Japanese researchers reported a proportion of isolates of *F. graminearum* from Japan that produced nivalenol (NIV) (Chart 3).[24] In our NZ collections of *F. graminearum*, we found an approximately even distribution of isolates that produced DON or NIV, recovered in acetylated forms because of the liquid culture conditions used. The DON-producers were predominantly of the 15-acetyl-DON chemotype.[19]

F. culmorum also is mostly reported internationally as a producer of DON. In our NZ isolates, we found no examples of this. Rather, the majority (>90%) produced

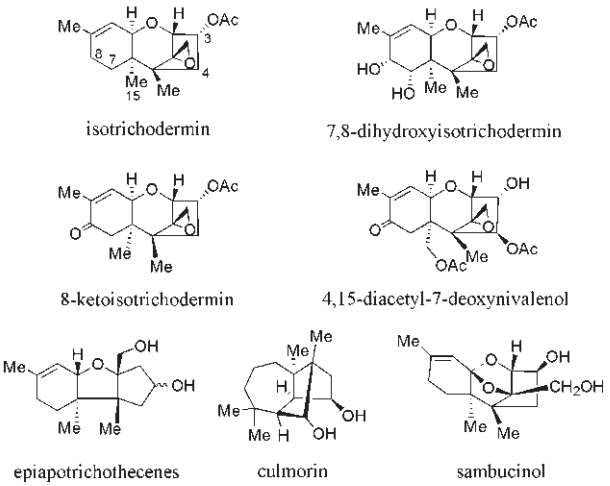
Chart 3. Common trichothecene structural types



NIV, expressed in the liquid culture media as 4,15-diacetyl-NIV and 15-acetyl-NIV.[19] Surprisingly, there was also a small number (4%) that produced 4,15-diacetoxyscirpenol (DAS) (Chart 3).[19] The isolates that produced this were confirmed as *F. culmorum*, although described as degenerate by taxonomists at the University of Sydney.

Trichothecene production by *F. crookwellense* had not been reported before our work as the species was first described only in 1982.[25] With the Agriculture Canada group, we were first to identify this species as a producer of NIV-type trichothecenes.[16,17] In these initial studies, a number of new trichothecene metabolites were isolated and identified as derivatives of isotrichodermin (Chart 4) and they represent early steps in the biosynthetic pathway to the NIV structure. A number of other related compounds (Chart 4) were also isolated. In a larger study,[19] it was found that 85% of NZ *F. crookwellense* isolates were NIV-producers expressed as 4,15-diacetyl-NIV and 15-acetyl-NIV in the liquid culture media; a small proportion (2%) were found to produce DAS. Subsequently, production of DAS by some Polish isolates of this species was reported.[26]

Chart 4. Selected metabolites of *Fusarium crookwellense*



The results of these studies led us to believe that the prime risk in NZ-produced grains would be from the trichothecenes NIV and DON, and from the estrogen, ZEN. There was likely to be a smaller risk from trichothecenes of the DAS and T-2 toxin (Chart 3) types. After 2-3 years of measurements, it was safely concluded that DAS and T-2 toxin occurred rarely in NZ-produced grain, and then at very low levels.[20] This allowed the focus to be on NIV, DON, and ZEN. DON and ZEN are common worldwide where *Fusarium* fungi infect grain crops, but the high incidence of NIV in NZ is relatively unusual. Were it not screened for here, a large proportion of the trichothecene mycotoxin risk to animals eating NZ-grown crops would not be determined. Some NZ laboratories offer commercial screening of grain using DON immuno-quick tests. The use of such a test is not truly valid in the NZ scene, as it does not determine the presence of the more toxic NIV.

Analytical Methods

Fusarium mycotoxins cover a wide range of polarities, tend to have generally low volatilities, and just a few have useful chromophores for either ultraviolet (UV) or fluorescence detection. While a raft of methods now exists for their analysis, in the mid-1980s, the most common method for trichothecene analysis was by gas chromatography with electron capture detection (GC-ECD) after derivatisation, typically with *N*-(heptafluorobutyryl)imidazole.[27] Published methods competed for the number of parent toxins and acetylated derivatives that could be determined within a single GC run.[28] For example, screens for DON might have included some, or all, of 3-acetyl-DON, 15-acetyl-DON, and 3,15-diacetyl-DON. At that time, the large research-grade GC-MS instruments were used for determination of complex mixtures such as those from culture studies, but they were not cost effective for routine measurements. ZEN, and its most common metabolites, α- and β-zearalenols (the epimeric alcohols derived from reduction of the keto group in zearalenone shown in Chart 2), could be determined by high performance liquid chromatography (HPLC) with fluorescence detection,[16] and NIV and DON could be determined by HPLC with UV detection.[29] However, for these three analytes and for trichothecenes in general, when in more complex mixtures containing related compounds, GC with a temperature gradient was preferred.[16,19]

Were the goal the measurement of mycotoxins in culture production experiments, then one could apply different techniques, as appropriate, for ZEN or for trichothecenes. It was often worthwhile to use a more complex method such as GC-MS in order to reveal structural variations and co-produced products. Liquid chromatography mass spectrometry (LC-MS) is now among the techniques commonly used for mycotoxin measurement, and it is particularly useful for qualitative analysis of complex extracts.

Despite these advances, a problem still exists for routine measurement and monitoring of grain contamination, namely, to decide how many toxins and related derivatives to screen for. Not all derivatives are commercially available, and each additional analyte adds extra cost and complexity. Following early work by Rood, Buck and Swanson,[30] we addressed this problem in our laboratory by developing a robust and reliable method that reduces all trichothecene derivatives to the parent alcohols prior to analysis.[31] In this way just two components (NIV and DON) are determined by HPLC and they effectively screen for the presence of the (at least seven) parent trichothecenes and acetyl derivatives occurring naturally. Similarly, using GC to measure NIV, DON, T-2 tetraol (dealkylated T-2 toxin), and scirpentriol (deacetylated DAS), we can determine the toxin challenge from all ma-

jor trichothecenes and related acetates. This approach also accounts for the presence of conjugates such as DON-3-glucoside, which occurs in barley, malt and beer.[32]

How was the Information Used?

Once the actual risk to NZ grain was established as primarily from contamination by NIV and DON, with an associated risk from ZEN, our primary targets for research studies were to understand the risk, define the issues, and propose solutions, focusing on these three compounds. By applying accurate quantitative chemical analysis, and concentrating on these three toxins, we were able to complete multiple applied research studies. They covered aspects such as the determination of the main crops at risk from mycotoxin contamination,[20] of the effects of harvest dates and hybrid or cultivar on contamination of maize and/or wheat,[33] of how infection and toxin contamination develop in maize crops,[34] of which fractions from harvested maize were most contaminated,[35] and of the effects of food processing on mycotoxin contaminants.[36]

Dissemination of the results of the studies led to a heightened industry awareness of mycotoxins in maize, the most at-risk crop, and changes were made to minimize their impact. These changes have included earlier harvesting, evaluating new hybrids for susceptibility to mycotoxin accumulation, and a better placement of available hybrids to fit local environments. Many of these changes were led by Genetic Technologies Ltd., the NZ producers of Pioneer® brand seeds. They greatly assisted much of our research by providing *in-kind* collaboration, and by allowing access to their field research sites.

The specialist research knowledge and skills gained during these studies were, and still are, scarce internationally, and this led to collaborative involvement in a number of interesting projects on fusaria. Some of these more research-driven projects and collaborations include the impact of co-occurring fungi and biocontrol organisms on mycotoxin production,[37] an assessment of the toxigenic potential of *F. tumidum* (a candidate bioherbicide for gorse and broom[38]), a determination of the toxigenic potential of new species and subspecies of *Fusarium* isolated in Australia,[39] and molecular phylogenetic analysis of NZ species.[40] There were also interesting manipulative chemistry studies in projects aimed at developing trichothecene conjugates for antibody production[41] for specific or generic immunoassay systems.

The Future

Who knows? All mycotoxin research has fallen on hard times over the last decade because the funding streams have ended. Accordingly, there is limited or no maintenance of a research capability, although routine testing laboratories do offer a screening service for selected compounds. It is, therefore, inevitable that lessons learnt in the 1985-2000 period will become diluted over time. It is to be hoped that *when*, in the future, the inevitable contamination outbreak happens, the lessons learnt in the past are not overlooked. Generalized screening for the latest buzz-contaminant will never address the real risk from what may well be a specific local contaminant produced under local conditions. If, as expected, the effects of global warming work to modify the dominant plant pathogens infecting crops in parts of the country, then new mycotoxin challenges for NZ could emerge in those regions.

Acknowledgement

I wish to thank all those who have helped to produce the work described or referred to here, most of whom are represented as co-authors in the citations. Much high quality work was performed with limited funds, some of that sourced through the NZ FRST. Especial thanks must go to Dr Margaret di Menna, ONZM, whose invaluable microbiological work provided a solid foundation for these studies, even long after she had officially retired. I also thank the visionary leaders in Genetic Technologies Ltd. for their early and continued support of this work.

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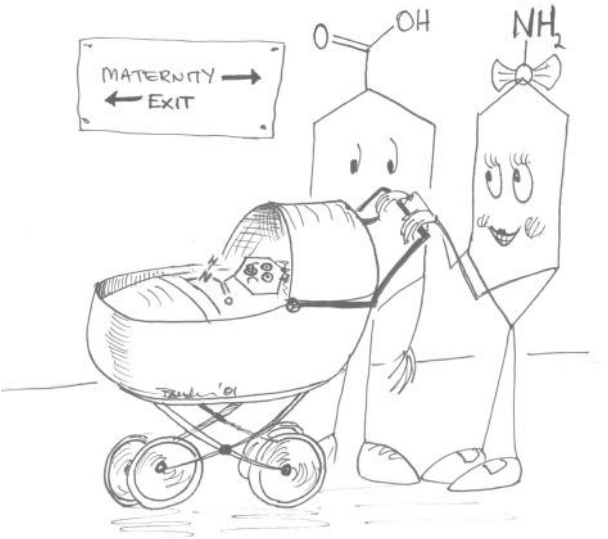

Brendan Burkett

Article

Cycloaurated Gold(III) Complexes – Possible Alternatives to Cisplatin?

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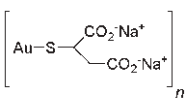
Gold in Medicine – A Brief Introduction

The serendipitous discovery of the anti-tumour activity of *cisplatin* [*cis*-$PtCl_2(NH_3)_2$] in 1969 has led to increased interest in the development of new metal-based anti-cancer drugs. However, regardless of the large numbers of new metal-containing compounds generated, many of which demonstrate anti-tumour activity, *cisplatin* still remains one of the most widely used anti-tumour drugs in the western world.

The similarities between gold(III) and platinum(II) (both are d^8 and form four-coordinate square planar complexes) give rise to the possibility of developing gold(III) analogues of *cisplatin*. The use of gold and its compounds in medicine is not a novel concept – ancient Arabic, Indian and Chinese physicians used gold preparations for the treatment of a wide variety of ailments. In 1890, Koch demonstrated that $[Au(CN)_2]^-$ has bacteriostatic effects, and in the 1920's gold compounds were used for the treatment of tuberculosis but later shown to be ineffective. Today gold(I) thiolates, namely Myocrisin® (sodium aurothiomalate) **1** and auranofin (aurothioglucose) **2**, are used for the treatment of rheumatoid arthritis (*chrysotherapy*). In addition, gold complexes continue to be screened for activity as anti-HIV, anti-microbial and anti-malarial agents. Several comprehensive reviews are dedicated to the medicinal applications of gold compounds and readers are directed towards these for a full and interesting history of the topic.[1] A large number of gold complexes also have been screened previously for anti-tumour activity, the details of which can be found in selected references.[2-4] However, despite promising results, no gold complexes have made it into clinical use as anti-tumour agents yet, although there continues to be a large quantity of research devoted to the development of new gold drugs. This article summarizes work conducted with neutral cycloaurated complexes and details some that has been conducted recently with gold(III) complexes in our Department.



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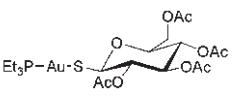

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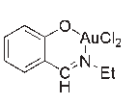
Cycloaurated Compounds as Anti-tumour Agents

The major set-back in the use of gold(III) in medicine is that it has a large reduction potential and is relatively easily reduced to gold(I) or gold(0). This is a potential problem in the body because of the presence of reducing thiol moieties, *e.g.* in the amino acid cysteine $HSCH_2CH(NH_2)CO_2H$. This problem seems to be largely overcome by incorporating the gold into a metallacyclic ring. If a chelating monoanionic ligand (L) is used, the resulting complex will have the general formula $LAuX_2$, where X is typically a unidentate anion such as Cl^- (examples of bidentate dianionic ligands are known – see below). Thus, the use of these types of systems provides a complex that remains neutral with four-coordinate square planar geometry as is seen in *cisplatin*. In addition, the presence of the chelating ligand forces the two anionic (Cl^-) ligands into a cis arrangement that further increases the similarity to *cisplatin*.

Initial studies on cycloaurated systems centred on those containing bidentate *N*,*O* donor ligands – either salicylaldimine-derived Schiff bases or pyridine-2-carboxylate as in **3** and **4**, respectively. However, the results were not promising as the complexes underwent immediate reduction to elemental gold in the presence of biological media that, presumably, was accompanied by oxidation of cellular material giving a disastrous toxicity.[5] Later, independent studies demonstrated that these compounds did display some level of cytotoxicity,[6] possibly from binding to DNA,[7] although other mechanisms could not be excluded - see below.



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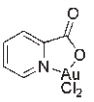

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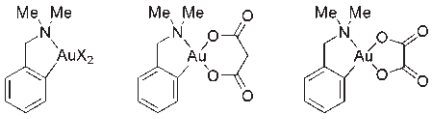
Most work conducted with cycloaurated organometallic complexes has centred around (damp)$AuCl_2$ [**5**; damp = 2-(*N*,*N*-dimethylaminomethyl)phenyl]. As in *cisplatin*, the metal atom is square-planar with two labile chloride ligands. Additionally, gold(III) is a relatively soft metal centre so that the softer (relative to *N*,*O* above) *C*,*N* ligand system stabilizes the metal towards reduction. Parish, Fricker and co-workers[8-10] initially investigated the *in vitro* anti-tumour activity of **5** against a range of human tumour cell lines and found that it was comparable to *cisplatin*, a control in the experiment. Like *cisplatin*, **5** showed greatest toxicity against breast (ZR-75-1), bladder (HT1376) and ovarian (SK-OV-3) cell lines. Because **5** showed good activity *in vitro* towards the breast tumour line it was also evaluated against a solid form of the tumour, grown as a xenograft in nude mice. The results indicated that **5** possessed modest anti-tumour activity as it reduced the size of the tumour, but there was also evidence of cytotoxicity; several mice died before the conclusion of the experiment. Overall, the results were not as promising as the initial *in vitro* screening predicted, possibly because the low solubility of the compound in aqueous media hindered its transport from the injection site to the tumour.[8]

In light of these results, it seemed likely that analogues of **5** with enhanced aqueous solubility characteristics would show increased activity. Replacement of the chloride

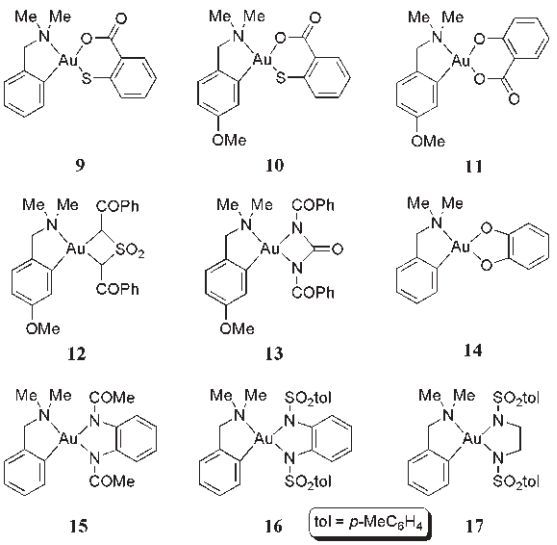


5, X = Cl
6, X = OAc

7 **8**

ligands by acetate, malonate or oxalate groups gave complexes **6-8**, respectively, which have better solubility. An added attractive feature of the acetato **6** is that, like *cisplatin*, the two labile ligands are hydrolysed in aqueous solutions.[9] Thus, **5-8** were evaluated *in vitro* against a panel of human solid tumours and, consequently, the bladder carcinoma (HT1376) was consistently the most sensitive to the new gold(III) complexes. In a similar manner to that described above, the complexes were evaluated *in vivo* against a bladder cell (HT1376) xenograft. Diacetato-**6** and malonato-**7** complexes showed activity similar to that of *cisplatin*; dichloride precursor **5** showed reduced activity and the oxalato derivative **8** was inactive, again possibly because of reduced solubility. In addition, acetato-**6** was also found to be active against the *cisplatin*-sensitive PXN/109/TC tumour albeit less so.[10]

As gold(III) is considerably more labile than platinum(II), it was suggested that compounds containing ligands bound fairly tightly to the gold centre may exhibit enhanced activity.[11] Therefore, Henderson and co-workers synthesized a range of bis-metallacyclic compounds that, in addition to the original damp metallacycle, contained a second metallacyclic ring produced upon substitution of the two chloride ligands with dianionic thiosalicylate,[12] salicylate,[12] aurathietane dioxide,[11] ureylene,[13] catecholate[14] or amidate[15] ligands. The anti-tumour activity was evaluated *in vitro* against the P388 murine leukemia cell line and the results are presented in Table 1. The activity is reported as an IC_{50} value, which is the concentration (μM) required to reduce the cell growth by 50%; smaller concentrations equate to a higher activity. In particular, thiosalicylate-**10** and catecholate-**14** show good anti-tumour activity, and derivatives containing these ligands could benefit from further study. In addition, the complexes carrying a methoxy substituent on the phenyl ring of the damp ligand show better activity than their unsubstituted analogues, *cf*. **10** *vs* **9**; this is possibly because of increased solubility.



9 **10** **11**

12 **13** **14**

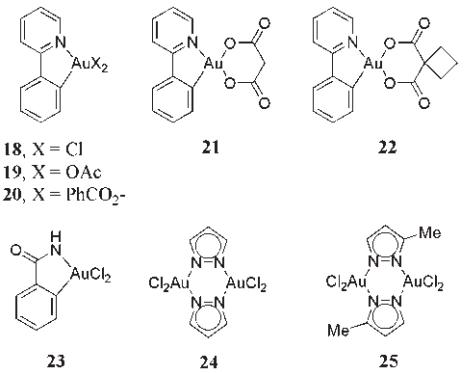
15 **16** **17**

tol = *p*-MeC_6H_4

Table 1. The anti-tumour activity (P388) of selected gold(III) metallacycles

	IC_{50} (μM)		IC_{50} (μM)
9	4.01	**14**	0.46
10	0.59	**15**	14.5
11	10.2	**16**	6.68
12	0.70	**17**	1.09
13	12.9		

Other cycloaurated complexes that have been evaluated for anti-tumour activity *in vitro* are **18-22**. These contain the related *C*,*N* co-ordinated 2-phenylpyridine ligand. The activity against MOLT-4 (human leukemia) and C2C12 (mouse tumour) cell lines indicated that the gold complexes were more active than *cisplatin* against the MOLT-4 cell line. However, with the exception of **22** they were inactive towards the C2C12 cell line.[16] Gold(III) complexes that contain monoanionic *N*,*N*'-chelating ligands, *e.g.* picolinamide **23**, or two bridging pyrazolide ions **24** and **25** have also been evaluated against the MOLT-4 and C2C12 cell lines; the results indicate that the complexes have activity comparable to *cisplatin*.[17]



18, X = Cl
19, X = OAc
20, X = $PhCO_2$-

21 **22**

23 **24** **25**

Mechanistic Considerations

It is well established that the molecular target of *cisplatin* is DNA. After *in vivo* hydrolysis of the chloride ligands (to form a species such as $[PtCl(NH_3)_2(H_2O)]^+$), the complex binds to adjacent nitrogen atoms (N-7) of guanine residues forming intra-strand crosslinks. Hydrogen bonding between *cisplatin* and phosphate groups on the DNA backbone may aid the interactions. It seems unlikely that the gold(III) complexes will interact with DNA in the same fashion as some show activity against *cisplatin* resistant cell lines. In a series of experiments, it was shown that reaction of the damp acetate-**6** with *N*-donor nucleosides, such as guanosine, gave non-quantitative binding and, in addition, the coordination was to alternative nitrogen atoms, *viz*. not N-7.[9] Later, a series of detailed experiments conducted by Parish and Fricker (also with **6**) demonstrated that this complex, and by inference other damp analogues, reacts by way of a different mechanism from that for *cisplatin*, and that DNA may not be the target molecule.[10]

An alternative molecular target for gold(III) complexes may be cathepsin B, a cysteine protease that is implicated in the pathophysiology of a variety of diseases including cancer. Although the exact role of cathepsin B in solid tumours is not fully known, it is thought to be involved

in tumour metathesis, angiogenesis, and tumour progression. As gold drugs are known to react with thiols, the interaction of gold(III) complexes with cathepsin B was investigated and, indeed, the gold(III) damp complexes - and related six-membered ring analogues - were shown to be moderate inhibitors of the enzyme. Binding of the gold complexes to the enzyme was tight, but reversible and this is preferable in a drug candidate. Recently, it has been proposed that gold(III) complexes have anti-microbial effects, possibly by inhibiting the enzyme thioredoxin reductase.[3]

Current Research at Waikato

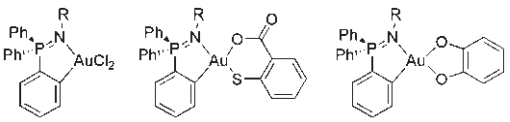
We have become interested in developing new metallacyclic systems that contain a gold(III) metal centre because of the promising anti-tumour activity displayed by certain of the gold(III) complexes described above. We have prepared a series of new compounds and subjected them to preliminary *in-vitro* screening against the P388 murine leukemia cell line.

Cycloaurated Phosphorimine Systems

Phosphorimines are ligands that, like damp, coordinate to the gold centre through carbon and nitrogen. Because of the similarity of these complexes to the damp systems described above, a selection of gold(III) iminophosphorane complexes, along with their thiosalicylate and catecholate derivatives, were screened for anti-tumour activity against the P388 murine leukemia cell line.[18,19] The results appear in Table 2.

Table 2. The anti-tumour activity (P388) of selected gold(III) iminophosphoranes

	IC_{50} (μM)		IC_{50} (μM)
26	10.7	**29**	0.97
27	33.4	**30**	<0.74
28	<0.69	**31**	1.03

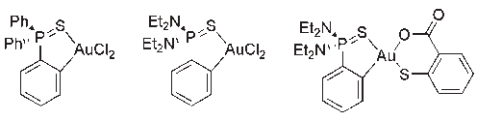


26, R = **Ph** **28**, R = Ph **30**, R = Ph
27, R = **Bu^t** **29**, R = Bu^t **31**, R = Bu^t

The series of complexes that contain a phenyl substituted iminophosphorane ligand, namely **26**, **28** and **30**, are consistently more active than the analogues **27**, **29** and **31** that carry a *t*-Bu substituent. In addition, the thiosalicylate or catecholate derivatives **28-31** show a *ca*. ten-fold increase in activity over the dichloride precursors. The IC_{50} values of **30** (<0.74 μM) and **28** (<0.69 μM) are comparable to the analogous damp complexes **14** (0.46 μM) and **10** (0.59 μM), respectively. This indicates that changing the cycloaurated precursor and introducing a phosphorus into the metallacyclic ring, whilst slightly altering the electronic and steric properties, does not significantly change the activity of the complexes.

Cycloaurated Phosphine Sulfide Systems

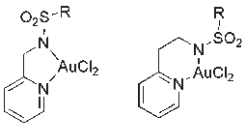
Complexes **32-34** are a unique class of cycloaurated complexes in that the neutral donor ligand is ***not*** nitrogen; they also contain a ligand coordinated to the gold centre that is potentially reducing. These complexes were screened to see if changing the neutral donor ligand had any significant effect on the anti-tumour activity. Compound **32**, which contains a cycloaurated triphenylphosphine sulfide moiety, is essentially inactive against the P388 murine leukemia cell line (IC_{50} >22 μM). Compound **33**, in which the two free phenyl rings of **32** are replaced by NEt_2 groups, was much more active (IC_{50} = 6.31 μM), possibly because of increased solubility. As with the above, thiosalicylate-**34** again is somewhat more active (IC_{50} = 2.4 μM).[19]



32 **33** **34**

Cycloaurated Pyridylsulfonamide Systems

The *N*,*N*-coordinated system no longer contains a carbon-gold σ bond but instead a σ (pyridyl)nitrogen-gold bond, analogous to cycloaurated picolinamide **23**. Although **23** had promising activity against MOLT-4 and C2C12 cell lines, the anti-tumour activity of complexes **35-39** was poor as all had IC_{50} values > 22 μM. These complexes are not as stable as the *C*,*N* counterparts as they undergo reduction with mild reducing agents such as phosphines; this may well be a factor in the poor biological activity of these complexes.[20]



35, R=tol **38**, R=tol
36, R=Ph **39**, R=Ph
37, R=Me

Concluding Remarks

The structural similarities between gold(III) and platinum(II) suggest that there is a possibility to develop gold analogues of the prominent anti-cancer drug *cisplatin*. Despite promising results from early preliminary screenings, no gold drugs have made it into clinical use. The gold(III) complexes synthesized in our laboratories contain a carbon-gold bond and show promising anti-tumour activity against the P388 murine leukemia cell line. This is especially so when the dichloride ligands are replaced with chelating dianionic ligands such as thiosalicylate or catecholate. In addition, the iminophosphorane ligand is easily tuned to increase desirable properties in the final complex, and work is currently underway to investigate more water soluble derivatives. Further studies on these compounds, especially the more water soluble variants and their thiosalicylate and catecholate derivatives, will include testing against other cell lines. When the neutral donor ligand is changed from nitrogen to sulphur the activity decreases and if the complexes contain no carbon-gold bond, *e.g.* with *N*,*N* cycloaurated ligands, complete inactivity is recorded.

Acknowledgements

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PACIFICHEM 2010

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A recent meeting of the organizing committee finalized the conference programme which will contain over 230 separate symposia. These are to be scheduled in over 1000 separate sessions of oral or poster presentations. A student poster competition will be held where 200 finalists will be indentified on the basis of a submitted abstract and the 50 winners will be selected by on-site interview and poster discussion.

A key difference from previous Pacifichem congresses will be the inclusion of the Hawaiian Conference Centre as well as the traditional beachfront hotels as conference venues. This will allow for large participation poster sessions with the possibility of accommodating large common-interest groups at the same time. This approach has been successfully used at some recent ACS national meetings.

For updated information about the various symposia, participation notes and deadlines please view the website:

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For further information about this conference please do not hesitate to contact the NZIC representative: Prof. Rob Smith (*rajsmith@chemistry.otago.ac.nz*, phone 03 479 7924).

Article

The Quest for Extreme Water Repellency: Superhydrophobicity Made Easy

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The Interaction of Water with a Surface: An Introduction

In his seminal work *On Floating Bodies I* Archimedes of Syracuse provided an explanation of the action of solid bodies on water.[1] Although his thesis immediately benefitted King Heiro II[2] and has continued to serve mankind well, it ignores the effect of the interfacial interactions between the solid, water and air (surface tension). These interactions are negligible, or at least are considered negligible, compared to forces arising from the effect of gravity on large bodies. However, as the mass of the body decreases, the surface interactions become increasingly important leading to some unusual and potentially useful phenomena. The understanding and application of these effects is currently driving much fundamental research by physicists, chemical engineers, material scientists, and chemists into surfaces that display extreme properties, in particular extreme water repellency, or *superhydrophobicity*. It is only comparatively recently that detailed mathematical expressions for the interaction between a liquid, solid and gas at these extremes have been developed, making progress that parallels that for the fabrication of these surfaces.

When a drop of liquid comes into contact with a flat solid surface the outcome is determined by the interfacial free energies between surface and gas, between liquid and gas, and, most importantly, between surface and liquid. If the net interaction between liquid and solid is attractive then the drop will tend to spread out and increase the area of contact (or, more correctly, increase the length of the boundary between all three phases), and if it is repulsive then the drop will tend to bead up so as to decrease the area of contact (decrease the length of the boundary line between all three phases). Provided the volume of the drop is sufficiently small that the effect of gravity on its shape is negligible, then the liquid typically adopts the shape of a truncated sphere. This can be described by the contact angle (θ) which is the angle defined by the surface and the tangent of the liquid droplet at the point of contact of all three phases as shown in Fig. 1. The contact angle is related to the three interfacial free energies according Young's relation:[3]

$$\cos\theta = (\gamma_{\text{surface-gas}} - \gamma_{\text{surface-liquid}})/\gamma_{\text{liquid-gas}}$$

where $\gamma_{a\text{-}b}$ is the interfacial free energy per unit area (force per unit length) between two phases a and b.

This can be rewritten as the Young-Dupré equation:

$$\cos\theta = (\Delta W - \gamma_{\text{liquid-gas}})/\gamma_{\text{liquid-gas}}$$

where ΔW is the adhesion energy per unit area between the solid and liquid, and $\gamma_{\text{liquid-gas}}$ is the surface tension of the liquid. It is evident from this equation that, for surface-liquid combinations that are strongly attractive, the contact angle will be small: as $\Delta W \rightarrow 2\gamma_{\text{liquid-gas}}$ and $\cos\theta \rightarrow 1$. Conversely, when the surface is *hostile*, *viz*. there is little attraction, the contact angle will be large as $\Delta W \rightarrow 0$ and $\cos\theta \rightarrow -1$. It is also evident that for weakly attractive surface-liquid combinations, liquids with large surface tensions ($\gamma_{\text{liquid-gas}}$) will tend to give larger contact angles, since, when $\Delta W << \gamma_{\text{liquid-gas}}$ $(\Delta W - \gamma_{\text{liquid-gas}}) \approx -\gamma_{\text{liquid-gas}}$ Water has a high surface tension (*ca*. 0.072 Nm^{-1}) in comparison to other common solvents such as hexane (*ca*. 0.018 Nm^{-1}) and methanol (*ca*. 0.023 Nm^{-1}), and so typically gives higher contact angles with hostile surfaces.

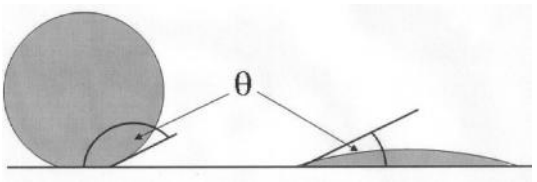

Fig. 1. Contact angles of a droplet on *phobic* and *philic* surfaces.

Most important liquid-surface phenomena and their applications, especially those in nature, involve water and air as the liquid and gas phases. The adjectives *hydrophobic* and *hydrophilic* have arisen to describe surfaces on which water beads up ($\theta > 90°$) and those on which it spreads ($\theta < 90°$) For more extreme contact angles the terms *superhydrophobic* and *superhydrophilic* have been introduced to describe surfaces that display contact angles of greater than 150° and less than 5°, respectively. These are arbitrary values that carry no special scientific significance, but they are universally accepted.

Nature provides us with some beautiful examples of superhydrophobicity. For example, pond skaters (genus *Gerridae*), lotus leaves and the fog-harvesting Namib Desert beetles all show exceptionally high contact angles (Table 1). It is clear from these examples that a low surface energy coating is essential to generate superhydrophobicity; Nature uses waxy organic molecules to provide this coating. Although organic polymers, such as polythene (*ca*. 30 mN m^{-1}), have lower surface energies than substrates such as metals and glass (*ca*. 45 mN m^{-1}), they are not as low as those of polyfluoroalkyl organics. Consequently, it might be expected that a compound such as polytetrafluoroethylene (Teflon®), the archetypal non-stick material, which has a surface free energy of 22 mN m^{-1} by virtue of the non-polar C—F bonds, would be at least as superhydrophobic as Nature's examples. However, the contact angle of polytetrafluoroethylene is meager in comparison (Table 1). Nature teaches us that roughness is also neces-

sary to generate superhydrophobicity. For example, pond skaters' legs have a hierarchical structure of nanogrooves in microsetae (tiny hairs), and it is this double roughness that dramatically enhances the contact angle.[4] The effect is also evident when polytetrafluoroethylene is roughened by treatment with oxygen plasma, although not to the same extent.[5]

Table 1. Representative contact angles

Material	*θ* / °
Pond skater's leg	167.6 ± 4.4
Lotus leaf	≈ 160
Namib Desert beetle	≈ 160
Polytetrafluoroethylene	116 ± 2
Polytetrafluoroethylene after plasma treatment	131 ± 4
Laser ablated polypropylene with sputtered polytetrafluoroethylene	up to 170
n-Perfluoroeicosane	≈ 119
Etched aluminium coated with polyfluoroalkylsiloxane	156
Etched copper coated with polyfluoroalkylsiloxane	153
Copper or zinc coated with silver or gold, coated with polyfluoroalkylthiol	173 ± 2
Copper coated with silver, coated with dodecanoic acid	156
Silicon wafers treated with methyltrichlorosilane	up to 180

Although very probably simplistic and approximate, it is commonly considered that two regimes operate for water on a rough surface. In the Wenzel state, the water is in contact with all the surface,[6] whereas in the Cassie-Baxter state the water rests partly on cushions of air trapped in surface cavities and touches the surface only at promontories (Fig 2).[7] For the Wenzel state the relationship between the contact angle and surface roughness can be quantified by the expression:

$$\cos\theta = r\cos\theta',$$

where θ′ is the contact angle for a smooth surface of the same material and r is the roughness factor, *i.e.* actual surface area/planar projection. More correctly, this is the actual length of the boundary between all three phases/the projected length of the boundary between all three phases on a smooth surface.[8] Although in practice it is very difficult to measure 'r' directly, the equation clearly indicates that if θ′ is greater than 90° then hydrophobicity increases with the amount of roughness. Roughness also enhances hydrophilicity if θ′ is less than 90°.

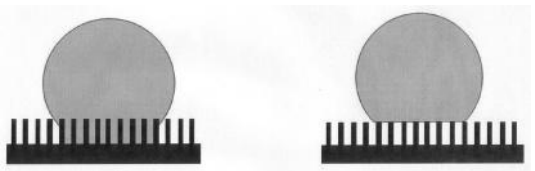

Fig. 2. Wenzel and Cassie-Baxter regimes.

For the Cassie-Baxter state the contact angle is given by:

$$\cos\theta = f_1\cos\theta' - f_2,$$

where f_1 is the fraction of liquid in contact with the surface and f_2 is the fraction sitting on air ($f_1 + f_2 = 1$). Although roughness is not explicit in this equation, it can be easily imagined that greater roughness will lead to more air trapped in surface cavities.

Although the contact angle is a useful parameter, it can be misleading and is difficult to measure at the extremes. It is calculated by line-fitting to photographs of the droplet and, as it is not always clear where the droplet touches the surface, a degree of subjective judgement is used. There is also often hysteresis in the contact angle for droplets as their size is altered. The difference between the advancing angle (that of a growing droplet) and receding angle (that of a shrinking droplet) also gives an indication of the degree of hydrophobicity. Another useful parameter is the roll off, or sliding angle. This is the angle through which the surface must be tilted before a sessile droplet will start to move and it is related to the contact angle hysteresis; a low hysteresis will give a low roll off angle and a large hysteresis will give a large one. The perfect hostile surface should display a contact angle of 180°, no contact angle hysteresis, and an immeasurably small roll off angle. Additionally, the surface should show no adhesion when it is lowered on to and lifted from a water droplet.[9]

Fabrication of extremely hydrophobic surfaces with θ approaching 180° previously has been tricky and expensive: The substrates are difficult to prepare, the processing involves specialized equipment such as plasma generators, and reproducibility can be problematic.[9,10] Furthermore, the surfaces are fragile, easily damaged, and cannot be repaired or regenerated readily. Consequently, potential applications have been limited to small-scale high cost technologies, such as microfluidic and lab-on-a-chip devices. Large-scale industrial applications have also been limited severely by the lack of methods of preparing superhydrophobic surfaces on metals. There are a small number of methods for coating metals with *e.g.* polyfluoroalkylsilicones, but prior preparation of the metal surface is required, which for some metals involves lengthy acid treatment. The surfaces are only just superhydrophobic (Table 1) and are easily damaged.

Easy Superhydrophobic Surfaces

The involvement of an inorganic chemist in this area arose when a colleague, Dr. Steven Bell, wished to use superhydrophobic surfaces for Raman spectroscopic experiments. Knowing of my background in fluorine chemistry, he approached me seeking assistance in making surfaces by etching a metal with hydrofluoric acid.[11] After etching, the metal was immersed in a solution of a polyfluoroalkylsiloxane formed *in situ* by aqueous methanol hydrolysis of a trialkoxysilane. Our results were disappointing. We wondered why this was the case, and we were particularly concerned that it was unclear how, or indeed if, the siloxane was chemically bonded to the metal. And so, with little knowledge of superhydrophobicity, or of other attempts to generate hostile surfaces, we naïvely set out to develop an alternative method.

It is well established that thioalcohols form self-assembled monolayers on gold and silver surfaces by way of covalent metal—sulfur bonds. Typically, past research focussed on well-defined smooth metal surfaces that are more amenable to study by a range of physical techniques, in particular ellipsometry. Indeed, a number of elegant studies have been performed to establish the packing of the thiols and structure-property relationships.[12] However, as these surfaces are smooth they do not display superhydrophobicity even if polyfluoroalkyl thiols are used. It is also well known that in the absence of a metal oxide coating, metals undergo spontaneous electrochemical oxidation with solutions of metal salts with more positive reduction potentials. In this way one metal may be galvanically deposited on another by simple immersion of the first in an aqueous solution of a salt of the other. For example, gold may be deposited on zinc [$E°$ (Zn^{2+}/Zn) = –0.763 V] by dipping a piece of zinc in a solution of tetrachloroaurate(III) [$E°$ ($AuCl_4^-/Au$) = +0.994 V]. Thus, it occurred to us that depositing silver or gold on a metal and then coating that with a polyfluoroalkylthiol may be a good place to start our investigation. The results were astounding![13]

Copper or zinc foil was immersed in an aqueous solution of silver nitrate or tetrachloroauric acid for *ca*. one minute, and then immersed in a dichloromethane solution of a thiol for five minutes. The contact angles of the surfaces were calculated conservatively as 173 ± 2° (Fig. 3), but since the roll-off angles were only 0.64 ± 0.04°, and no adhesion was observed when they were lowered onto and lifted from a water droplet, the surfaces can be regarded as almost perfectly hydrophobic. Furthermore, the surface free energies were calculated to be 1.00 ± 0.02 mN m^{-1}, a value significantly lower than that of pure fluorocarbons such as *n*-perfluoroeicosane (6.7 mN m^{-1}).[14] Scanning electron microscope studies showed that the surfaces had the necessary hierarchical structure. This resulted from the student, Iain Larmour, fortuitously selecting the correct combination of silver nitrate concentration and immersion time for the galvanic deposition; lower concentrations or shorter times would have given incomplete coverage of the metal or coatings too thin to give sufficient roughness, while higher concentrations or longer times would have given a thicker, but more uniform, smoother surface coatings.

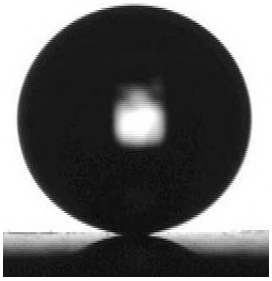

Fig. 3. An 8 mm^3 water droplet on zinc coated with silver, coated with polyfluoroalkylthiol.

This double immersion method is cheap, simple and quick. It is applied to metals and, as the surfaces may be readily repaired by repeating the process, it represents a technological leap in fabricating hostile surfaces. It is so simple that it has been adapted for a school experiment![15] Subsequently, it was found that 1-decanethiol gives surfaces that are almost as superhydrophobic as those formed by polyfluoroalkylthiol, reducing the cost and alleviating concerns about the possible toxicological effects of polyfluoroalkyl compounds. And it is not limited solely to superhydrophobicity! For example, superhydrophilic surfaces may be generated by using 6-hydroxyhexanethiol in place of the polyfluoroalkylthiol. The method has allowed us, and others, to investigate a range of phenomena and develop possible industrial applications.

Superhydrophobic Phenomena

Superhydrophobicity is responsible for a range of well-known phenomena, including self-cleaning by lotus leaves surfaces, meniscus-climbing by insects, and the combining of breathability and waterproofing in fabric. However, there are phenomena associated with superhydrophobicity that have been little studied because of the technical difficulties of preparing suitable surfaces. The double immersion method provides such surfaces, allowing the investigation of established and new phenomena, such as those described below.

Underwater Mirror

Only as recently as 2006 was it predicted that underwater superhydrophobicity was possible and thermodynamically stable,[16] and the double immersion technique has provided surfaces that have confirmed this. Superhydrophobic metal surfaces appear matt black in air and maintain this when submerged and viewed at or close to the perpendicular. However, when viewed at an angle of *ca*. 47° or less to the plane of the surface, they have the appearance of a mirror (Fig. 4). This arises from reflection off an air-water interface (critical angle 48.63°), as occurs with open areas of still water and bubbles of air trapped by aquatic insects, such as diving beetles. The presence of a layer of air over the surface is indicative of an extremely superhydrophobic surface in the Cassie-Baxter regime for which it is calculated that water touches less than 1% of the surface.

Fig. 4. Underwater mirror revealing blemishes (upwards from bottom left).

The mirror is useful for detecting defects in the surface, since these appear as dark spot or lines (Fig. 4). It might be expected that if the system is put under pressure the

surface will change from the Cassie-Baxter to the Wenzel regime, the onset of which will be evident from a disappearance of the mirror. It has yet to be established at what pressure this occurs, but the Cassie-Baxter regime is stable to at least 1.2 atm.

Mesh Boats and Archimedes' Principle

Metal objects with superhydrophobic surfaces experience more buoyancy than those without these surfaces. This stems from the more repulsive surface-water interfacial interaction. As pointed out previously, the net force is dependent on the boundary line between the three phases rather than the surface area. Consequently, a superhydrophobic metal mesh should experience more force than a piece of foil of the same mass. Furthermore, below a certain hole size of the mesh the water repellency of the surface should prevent water from passing through the mesh, unless pressure is exerted. The double immersion method readily allows the fabrication of hostile metal meshes, and with a polyfluoroalkylthiol coating, water will not pass through holes smaller than *ca*. 2.5 mm in diameter. Thus, small boats may be constructed of mesh, rather than metal sheets. It has been reported that small rectangular boats (up to 4 x 5 cm) constructed of copper mesh with pore sizes up to 0.25 mm coated by the double immersion method, but treated with dodecanoic acid rather than polyfluoroaryl thiol, were able to support loads up to 30 times their mass.[17] Since dodecanoate generates a much smaller contact angle (Table 1), larger loads and larger pore sizes are possible with polyfluoroalkyl- or alkylthiols. Likewise containers for holding water may be constructed of mesh.

A related phenomenon concerns superhydrophobic sheets that float beneath the surface of the water. If a flat metal sheet is sufficiently light and floats in water, it will depress the water surface. If mass is added to the sheet the depression will increase until a point at which water will flow on to its upper surface and it will sink. For most metals the top surface would not be noticeably below the level of surrounding water before this occurred. However, if the sheet's top surface is hostile then it can actually be beneath the level of the surrounding water to a depth of *ca*. 4 mm (Fig. 5). A consequence of this is that the volume of water displaced by the object can be much greater than the volume of the object. At first it may appear that Archimedes' Principle is violated but it should be remembered that, rather than simply concerning equality of volumes, the principle states that the net upward force on a submerged object is equal to the weight of the water it displaces. Consequently, the upward force on the sheet will be much greater with a superhydrophobic coating than without one. It is interesting to note that it is only the top surface of the sheet that needs to be superhydrophobic. A superhydrophobic lower surface would provide a thin air layer, the volume of which would displace an equal volume of water, providing an additional upward force.

The 'Cheerios' Effect

Metal powders can be conveniently coated by the double immersion method. Hostile powders are buoyant by virtue of the superhydrophobicity, and demonstrate a remarkable effect, namely that when spread across the surface of water the particles congregate rapidly to form a raft: a dramatic demonstration of the *Cheerios Effect*.[18] This common phenomenon, named after the observation that the hoops of the well-known breakfast cereal tend to clump together in a bowl of milk, has been known for some time,[19] but it has only recently received a detailed mathematical treatment.[20] The reason the superhydrophobic metal powder shows the effect so well, is that since the attractive force between two particles is proportional to

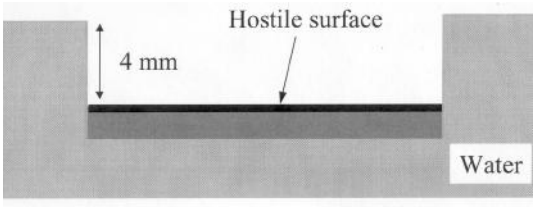

Fig. 5. Metal foil with a superhydrophobic top surface displacing more water than its volume.

$$[{}^{1}/_{3}\{2\rho_{particle}/\rho_{water} - 1\} - {}^{1}/_{2}\cos\theta + {}^{1}/_{6}\cos^{3}\theta]^{2},$$

the more dense the particles the greater the force - and metals (ρ: 8.96 g/cm^3) are considerably more dense than most floating objects, particularly cereal hoops. The strength of the force is reflected in the rapid formation of the raft, and its ability to support loads and wrap around objects when they are pushed downwards.[21]

Applications

Superhydrophobicity provides a wealth of applications. To date, most have been developed with non-metal substrates, *e.g.* anti-mist glasses, self-cleaning surfaces, breathable waterproof fabrics, non-fouling medical implants, microfluidic devices, *etc*. The ability to provide a superhydrophobic surface that can be repaired on a metal, especially on a large scale, opens up further important possibilities.

It has been established that a layer of air between a surface and water has important consequences for the motion of one relative to the other, namely the reduction of drag. There have been some attempts to realize this for marine vessels by designing hulls with *cavity cushions* or by pumping air microbubbles over the hull.[22] Studies on the latter found that there was a net energy saving of 5–10% in a trial with a 120 m vessel. By virtue of providing an air layer, hostile metal surfaces may have an important application in marine transport, for which even a small energy saving has a large financial benefit. Additionally, such surfaces are expected to be more resistant to biofouling, which can increase drag by 50% and necessitate regular expensive treatment in dock. Use in metal pipes carrying water is another potential application. As well as reducing drag, the superhydrophobic surface can protect the metal pipe from corrosion. This latter property also suggests these surfaces will be useful in industrial heat exchangers and condensers. Fouling is also a huge problem with medical metal implants especially urethral stents. Mineral encrustation and bacterial colonization can cause life-threatening conditions, and regular replacement, requiring

expensive surgery, can be traumatic and dangerous. The lack of contact between water and a superhydrophobic surface significantly reduces both mineralization occurring on the stent and colonization by bacteria.

Conclusions

Hostile, almost perfectly hydrophobic, metal surfaces can be prepared cheaply and quickly by a simple double immersion method. Imperfections can be readily identified using the underwater mirror and the surfaces can be readily repaired. It allows a range of phenomena to be investigated and opens up the possibility of large scale industrial applications that are being explored. It also provides some fun demonstrations, such as mesh boats and nets that can hold water. The method can be applied to provide other types of surface, *e.g.* superhydrophilic or reactive, by using an appropriate thiol. In conclusion, this innovation came from the collaboration of an inorganic and physical chemist to address a problem in surface science. Based on simple ideas, aided by some good fortune, the method has provided a welcome technological jump in the fabrication of hostile surfaces.

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Acetonitrile Supplies

Late 2008 through to early 2009, acetonitrile supplies became another victim of the economic downturn currently being experienced globally. Companies looked after their big customers, but others were put on backorders or rationed with supplies.

Acetonitrile is widely used as a solvent in High Performance Liquid Chromatography (HPLC). The shortage now seems to be over but prices continue to be volatile and many users are finding the price much higher than a year ago.

The shortages were blamed on a combination of factors. Acetonitrile is a by-product of the process to form acrylonitrile, which is used in a range of materials for a variety of goods including car manufacture. The economic recession has meant these materials are not required as much as previously, hence less acetonitrile is being produced. In addition a big acrylonitrile plant in Texas was affected by hurricane Ike and one or more plants in China were shut down during the Beijing Olympics. Also, it was hard to know how much stockpiling added to the shortage.

The response to this shortage saw many companies heavily promoting products to either reduce acetonitrile usage or provide alternatives. Some laboratories began transitioning to using other solvents like methanol, while others began looking at whether recycled HPLC waste was a viable option. It seems even now the shortage appears to be passed, alternatives are still being worked on or methods changed.

It is interesting to note this response compared to the change in petrol pricing a year ago and what the general population did in response. While petrol was not in short supply, the significant price jump did not seem to greatly alter society's dependence or use of petrol. Yet when a sector of the scientific community was affected by shortage and price hikes, there seems to have been a great deal of action and change in behaviour, even after the crisis was largely over.

Fast GC-MS and Chemometrics: Exploring Complex Mixtures

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Introduction

Increasing international trade has created a need for more increasingly sophisticated information on the qualitative and quantitative chemical composition of foods, as these define characteristics of quality,[1] authenticity,[2] ripeness,[3] storage conditions,[4] *etc*. The aroma and flavour for most food products, for instance, comprises a mixture of components ranging from a few to several hundred compounds. The changes that occur in the food matrix also play key roles in flavour perception, a decisive factor in the decision to purchase. Others important factors are associated with health claims,[5] such as the identification and quantification of compounds with beneficial or adverse health effects. Gas chromatographic separation combined with mass spectrometric detection (GC-MS) has become a very powerful tool in the study of complex samples of food.

Chromatographic separation methods are among the most frequently employed analytical techniques for compositional analysis,[6] and much effort has been invested in their development. Fast and efficient systems have evolved that now permit increased sample throughput and laboratory productivity, while reducing analysis cost. Fast chromatographic techniques aim to minimise time while maintaining reliable qualitative and quantitative results. Analysis times range from a few minutes for fast GC, seconds for very fast GC, and sub-seconds for ultrafast GC.[7] The usual peak widths at half height are 0.2-3 s in fast GC, 30-200 ms in very fast GC and 5-30 ms in ultrafast GC.

Numerous options exist for increasing the speed of capillary GC analyses. These can be classified into three general routes for faster GC separation.[8]

i) Minimizing the resolution to a value just sufficient for the analysis by:

reducing the column length; using columns with lower film thickness; higher initial/final temperatures and/or higher temperature programming rates; using above optimum carrier gas velocities; pressure/flow programming,

ii) Maximizing the selectivity of the chromatographic system by:

using a more selective stationary phase; applying coupled columns; using 2D-GC; detection; predominant utilization of MS detection, and

iii) Implementation of a method that reduces the analysis time at constant resolution by:

reducing the column inner diameter; using H_2 as the carrier gas; applying vacuum outlet conditions.

Nowadays in gas chromatography, mass spectrometry is widely used as a detection device but combining fast GC with MS detection is by no means trivial.[9] For an accurate description of a chromatographic peak in a chromatogram, at least 15-20 data points are required across the peak.[9] In the analysis of complex samples such as food, the use of fast GC-MS may face the challenge of having a large number of compounds with overlapping chromatographic peaks. In these cases, the number of points per peak is reduced making the analysis even more difficult. We have investigated analytical methods, based on chemometrics, to overcome difficulties posed in fast GC-MS from overlapping peaks and have found interesting results using multi-way analysis. We describe an application of this multi-way in which the model automatically predicts the presence of a profile of volatiles that has been confounded with very similar compounds. Potential applications for this modeling approach include the detection of multimolecular markers, *i.e. fingerprint*, for authenticity and fraud control purposes,[10] and geographical traceability of food products.[11] The fast GC-MS analysis corresponds to chromatographic runs of 3.8 minutes in a 20 m column with a 0.18 mm ID and film with 0.18 µm of thickness; 20 mass spectra are collected per second.

Chemometric and Multi-Way Analysis

Multi-way analysis was originally developed in psychometrics (study concerned with the theory and technique of educational and psychological measurement) between 1944 and 1980 where, among a set of models, two were found applicable to problems seen in analytical chemistry. These were the 1960's Tucker model[12] and *Parallel Factor Analysis* (PARAFAC) introduced by Harshman in 1970.[13] Independently, Carroll and Chang introduced *Canonical Decomposition* (CANDECOMP),[14] which is closely related to PARAFAC. In chemistry, Ho[15] introduced the Rank Annihilation Method to study fluorescence data in 1978; it is close to PARAFAC. Toward the end of the 80's and the beginning of the 90's, three-way methods were introduced to study liquid chromatography using ultraviolet spectroscopy (LC-UV) detection.[16] The number of applications of multi-way analysis in chemistry has increased since then due to the introduction and development of hyphenated instruments.[17] In general, these instruments produce a set of data with two or more dimensions per sample, *e.g.* GC-MS data are produced by collecting a mass spectrum for each retention time of chromatographic elution, producing for each sample a two-way array, *viz*. chromatographic and mass spectra, and when several samples are considered, a three-way array is produced (Fig. 1).

Multi-way analysis was introduced into chemistry to solve analytical problems involving complex samples containing several similar compounds with overlapping peaks that made the direct identification of the components very difficult. Three main areas of application were developed within chemistry as:

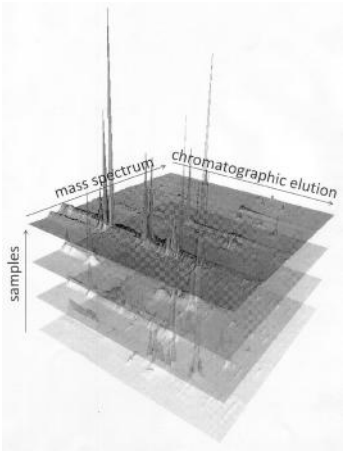

Fig. 1. GC-MS data as three-way array with chromatographic, mass spectra and samples ways.

i) Curve resolution.[18] This aims to separate the overlapped analytical signal between chromatographic peaks or between spectra in bi-dimensional spectroscopy, *e.g.* emission-excitation.

ii) Exploratory analysis.[19] Here the data are decomposed in modes as illustrated by Fig 1 that has three sets of two-way arrays that describe the samples. These describe the samples, the chromatograms, and mass spectra and are shown in Fig. 2.

iii) For quantification purposes the properties of the samples are now predicted directly from the multi-way data.[20]

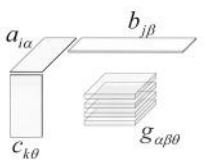

Fig. 2. Illustration of the decomposition of a three-way array using the Tucker model.

The application of these models in chemistry is based on the concept of additivity similar to Beer's Law in spectroscopy. In GC-MS, for example, an aliquot elutes from the GC column into the mass spectrometer at regular time intervals and generates a range of fragments, *i.e.* a mass spectrum. The signal with intensity $x_{m,t}$ that detects fragment *m* resulting from the eluting aliquot at retention time *t* is proportional to the sample concentration and to the mass of the fragment *m*; it is also proportional to its abundance in the respective mass spectrum and how easily the corresponding molecule can be fragmented.[21] This signal can be described as:

$$x_{m,t} = [conc] \cdot \varepsilon_m \cdot \pi_t$$

where [*conc*] is the concentration of the eluting compound in the injected sample, ε_m a factor proportional to the mass of the fragment *m*, and π_t a factor corresponding to the elution at time *t* [$\varepsilon_{(\bullet)i}$ represents the mass spectrum and $\pi_{(\bullet)}$ the chromatogram]. If the sample has a mixture of co-eluting compounds Y and Z, *viz*. overlapped peaks, the resulting signal is given by:

$$x_{m,t} = [conc]_Y \ \varepsilon_{m,Y} \ \pi_{t,Y} + [conc]_Z \ \varepsilon_{m,Z} \cdot \pi_{t,Z}$$

which represents the additivity of the measured signal. In general, for *N* co-eluting compounds the measured signal $x_{m,t}$ is given by:

$$x_{m,t} = \sum_{n=1:N} [conc]_n \varepsilon_{m,t,n} \pi_{m,t,n}$$

The additivity of the chemical signal allows the decomposition of a three-way array (Fig. 1) using the Tucker model[12] as given by Eq.1 and illustrated in Fig. 2:[19]

$$x_{ijk} = \sum_{\alpha} \sum_{\beta} \sum_{\theta} a_{i\alpha} b_{j\beta} c_{k\theta} g_{\alpha\beta\theta} \quad \text{..... Eq. 1}$$

In Eq. 1, x_{ijk} represents the intensity measured in the mass detector for ion mass fragment with mass *i* at the elution time *j* for the sample *k*, $a_{i\alpha}$ is the contribution of factor α to ion *i* (estimate of $\varepsilon_{(\bullet)}$), $b_{j\beta}$ is the contribution of factor β to elution time *j* (estimate of $\pi_{(\bullet)}$), $c_{k\theta}$ is the contribution of factor θ for sample *k* and $g_{\alpha\beta\theta}$ gives the factors describing the interaction between the *ways* of the data.

In curve resolution problems, the two-way array A, with elements $a_{i\alpha}$, has in its columns the mass spectra corresponding to each compound resolved from overlapped peaks. The two-way array B, with elements $b_{j\beta}$, has in its columns the chromatographic profiles for corresponding compounds in A; C gives the corresponding concentrations for resolved compounds. In problems involving exploratory data analysis, C will represent abstract factors and allow the identification of groups among samples.[19] A and B indicate which set of compounds make the difference between the detected groups of samples. In problems involving the prediction of properties of the samples, C is used to fit prediction models,[20] *i.e.* y = f(C), where y is the predicted property.

Example

A challenging situation in the analysis of GC-MS data with multi-way methods is the detection of a multimolecular marker (one with compounds in fixed concentration ratios) that has been confounded by the presence of similar compounds – the resulting chromatographic profiles markedly overlap. An experiment was designed to test the ability of multi-way methods to automatically detect the presence of *a fingerprint* using a multimolecular marker mixed with one of the confounding profiles. This is illustrated in Fig. 3. Our approach to detect the presence or absence of the multimolecular marker is illustrated in Fig. 4. Predictions above the broken line indicate the presence of the marker while points below the line suggest either the absence of the marker or its presence in levels lower than those defined by the model.

The model illustrated by Fig. 4 was developed with samples containing the marker confounded by profiles 2 and 3 of Fig. 3. The model was then applied to test a set of samples comprising the multimolecular marker mixed with differing proportions of confounding profile 1 that had a completely different chemical composition to the samples used to develop the model. The predictions made for these new samples shows the ability of the multi-way method to

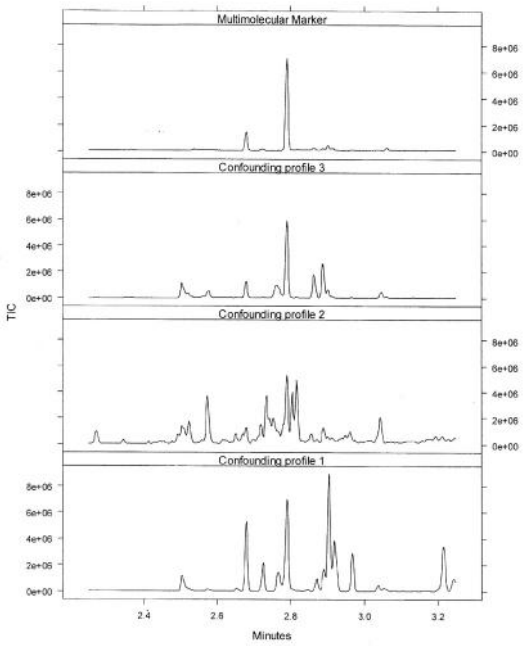

Fig. 3. Total Ion Chromatogram of a multimolecular marker and confounding profiles.

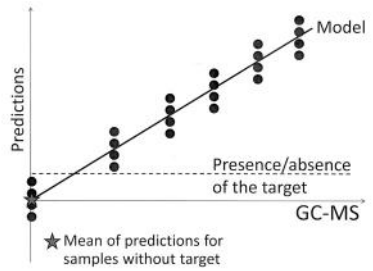

Fig. 4. The multi-way model defines a limit for the presence (or absence) of a multimolecular marker for points above (below) the broken line.

detect the presence of the marker in an unknown sample and are shown in Fig. 5; only three samples were classified incorrectly.

The multi-way model used to gain the predictions of Fig. 5 also generates a regression coefficient equivalent to regular linear models but in two dimensions, *e.g.* $y = \sigma x+\omega$ where σ is the regression coefficient. It represents the contribution of mass spectra and chromatographic modes (A and B) to the ability of the model to distinguish between the multimolecular marker and the confounding compounds. Fig. 6 presents the regression coefficient for the model described in Fig 5 and the GC-MS data for the multimolecular marker without confounding compounds. It indicates that the peaks discriminating between the confounding compounds and the multimolecular marker match the key peaks found in the marker. This particular property of the model is useful in identifying unknown multimolecular markers, *e.g.* a model is fitted to classify samples against two different geographical origins, and then the regression coefficient is used help in the identification of compounds related to discrimination between the origins.

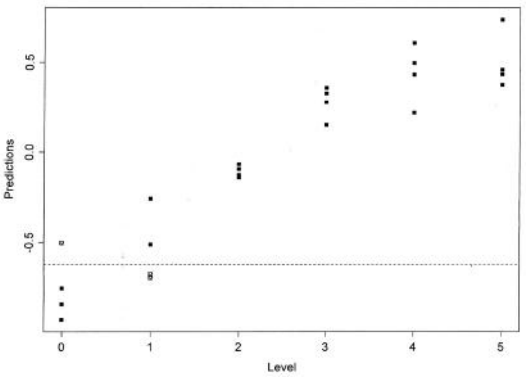

Fig. 5. Predictions of a multi-way model applied to a data set with a multimolecular marker at different concentrations, including samples absent in the marker.

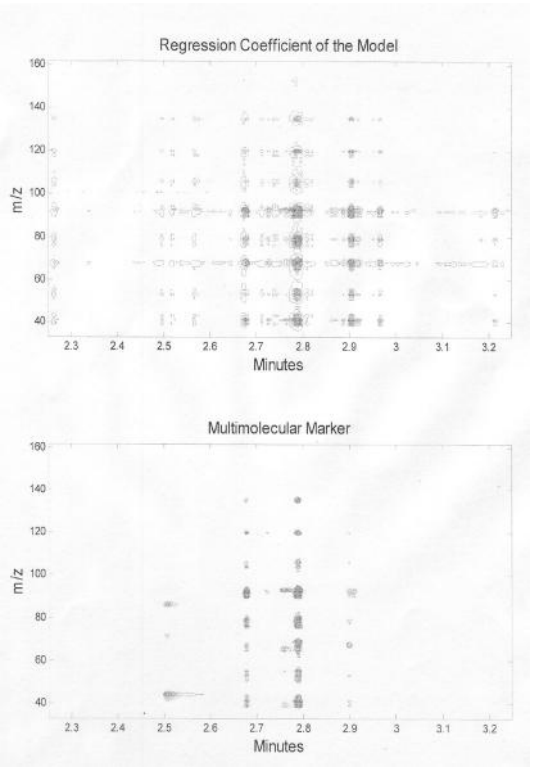

Fig 6. The regression coefficient for the model described in Fig 5.

Final Comments

The use of multi-way analysis combined with fast GC-MS is a powerful tool for analysing complex samples involving a large number of compounds with overlapping peaks. The example discussed illustrates this ability by using samples with the fingerprinting compounds mixed with confounding compounds. It considers the fingerprint as unknown to the model. In this particular application, the model is able to classify samples automatically based upon the presence of an unknown fingerprint and provides information helpful to identify the fingerprinting compounds. These are features that allow use of the model for authenticity, fraud control purposes, and geographical traceability of food products.

Acknowledgements

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Inventors Receiving their Just Rewards?

Katherine Hebditch and Jarrod Ward

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In a recent decision from the High Court in the United Kingdom (UK),[1] two inventors have been awarded a combined total of 1.5 million pounds compensation for contributing to a patent which proved to be of an "outstanding benefit" to their employer.

Background

An employer's right to ownership is specifically covered in the UK Patents Act which also states in sections 40 and 41 that an employee (as the inventor) is entitled to a compensation award where the employee has made an invention that is of an *outstanding benefit* to the employer.

It is well established in New Zealand that if an employee makes an invention during the course of their work duties then, in the absence of any other agreement to the contrary, the patent covering that invention will belong to the employer.[2] Unfortunately for employees in NZ however, there is no *outstanding benefit* provision in the NZ Patents Act.

What was taken into consideration when awarding the payout?

Sections 40 and 41 of the UK Patents Act have been in place (in slightly varying forms) for 30 years, but this is the first occurrence of compensation actually being awarded to an employee.

The two claimants, Duncan Kelly and Ray Chui, were employed by Amersham International Plc, which later became GE Healthcare Ltd. Their research efforts were aimed at synthesising phosphine compounds for use in radioactive heart imaging. The result was a product called *Myoview* which, following launch in the UK, Japan and the US, earned an estimated £1.3 billion up to 2007.

Under section 40, in order for the employees to be successful in their claim, they had to show that the patent was of outstanding benefit to the employer. Therefore in this case, it was not the value of the invention *per se*, but the value of the patent that covered the invention that was considered by the Court.[3]

In considering whether compensation should be paid to the employees, the Court considered several aspects of the situation. These included:

- if there was actual *outstanding benefit* to the employer;
- what the contribution of the employer was, *e.g.* the research costs and risks supported by the company;
- what the contribution made by the employees claiming compensation was, *e.g.* were they working independently, in a small team, or as part of a large team?

In this case the relatively small research costs incurred by the employer were recovered in the first year of sales of the product. The Court also looked at the compensation

already received by the employees in the form of salary, bonuses, and promotion. After considering these points and the values of the patents, the Court decided that it would be *just* to award compensation.

When considering the actual value of the patents, the Court considered a hypothetical scenario in which the patents had not been granted and contrasted this with the actual situation. In the hypothetical scenario, the product could still have gone to market, but without the monopoly afforded by the patents. The Court considered there to be two main advantages of the actual situation in comparison to the hypothetical one:

1. The price that can be charged for the product in the absence of competitors; and
2. Corporate success in deals by Amersham to acquire stakes in other pharmaceutical companies (it was considered that without the patents as assets, these deals would not have been achieved or at least not under such favourable terms).

The Court considered the first point to be the most important factor, and went on to value the amount of compensation due to the employees using an estimate of the increase to profits due to the absence of competitors.

The calculation of the award

The Court considered the number of potential competitors in the market, for example in the US, and found that there was unlikely to have been any competition until regulatory data exclusivity had expired. Therefore, it was only profits from the sales of Myoview after the expiry of data exclusivity that would have been beneficially affected by the presence of the patents. This was estimated to be half the total sales. It was estimated that the sales would drop by ~10% if competitors had entered the market. By taking a round figure of £1 billion for sales of the product, the value of the patent was found to be 10% of half the sales of the product, which gave a figure of £50 million. After considering the contribution of each of the inventors the Court awarded 2% of this figure to Dr Kelley (£1 million) and 1% to Dr Chiu (£500,000). In the context of the total sales figures, the compensation appears conservative. The total compensation paid out is estimated to be only three days profits from the sales of Myoview. It is interesting to note though, that neither party has appealed.

Would a similar law be beneficial in New Zealand?

This case concerned a section of British Patents Act which is not present in the current NZ Patent Act. There is a Patents Bill currently before Select Committee and there is a possibility that such a provision could be added at a later stage of the legislative process. Would such an addition make it fairer for employees making exceptional contributions, or would it place an additional burden on NZ businesses trying to compete in the world marketplace? This is a difficult question to answer, however it is question that, at least in Britain, has been answered positively.

An observation: one thing that this case highlights is the value of having patent protection for key products. The two main advantages of the actual situation in comparison to the hypothetical one that were considered by the Court in this case are clearly valuable advantages for any company to have. In the absence of patent protection those advantages would be lost.

A reminder: if you have any queries regarding patents or patent ownership, or indeed any form of intellectual property, please direct them to:

Patent Proze
Baldwins Intellectual Property
PO Box 852, Wellington
Email: *email@baldwins.com*

1 *Kelly and others v GE Healthcare Ltd* [2009] EWHC 181 (Pat)

2 Empress Abalone Ltd v Langdon [2000] 1 ERNZ 147 and [2000] 2 ERNZ 53 (CA)

3 This section was amended by the Patents Act 2004 to make compensation payable when the *invention* or patent (or combination of both) is of outstanding benefit to the employer, but this will only be applicable to patents applied for after 1 January 2005.

Katherine Hebditch and Jarrod Ward of Baldwins Intellectual Property specialise in chemistry and biotechnology patents. Katherine obtained her PhD in organic chemistry from the University of Manchester in the UK in 2004. She is currently studying towards registration as a patent attorney. Jarrod obtained his PhD in chemistry from the University of Auckland in early 2008. He is currently studying towards a law degree and registration as a patent attorney.

Article

Penicillins: Their Chemical History and Legal Disputes in New Zealand

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Introduction

In 1928, Sir Alexander Fleming showed that *Penicillin notatum* inhibited the growth of *Staphylococcus* cultures,[1-3] and that it had antibacterial properties *in vitro* and did not appear toxic in rabbits and mice.[4] Despite this, the use of penicillins, as a practical aid in overcoming bacterial infection *in vivo*, was not considered for many years, despite the concept of antibiotics having been appreciated as early as 1887.[5] Real interest in penicillin did not come until the late 1930s[4] when academia and industry, *e.g.* Merck, became involved.[5] This led to the isolation and study of an impure form of penicillin in 1940 by Florey *et al*.,[6] who showed that its subcutaneous use was highly effective against streptococcal infection in mice. This demonstration revived interest in the possible therapeutic use of penicillin in humans,[4] and further work from these authors allowed for the mass production of penicillin in WWII and its general use from 1949.[5] Eventually, biosynthetic 6-aminopenicillanic acid (6-APA; **10** below) was isolated by the Beecham Group[7] in 1957 and now is a common precursor to semi-synthetic penicillins.[8]

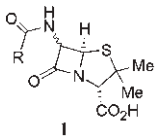
Florey's group at Oxford University did not patent their penicillin-related work, despite some members wanting it. In the 1950s, institutions such as Oxford lacked the facilities to progress intellectual property protection.[5] However, the Beecham company took full advantage of intellectual property rights, patented 6-APA, and have remained vigilant in its protection since. Over the fifty years since the initial patent, they have patented many variations, different semi-synthetic penicillins and related compositions.

This article provides a chemical history of penicillin, how it functions in biological systems, and how it has been developed since its initial discovery. It briefly expounds and comments on the patents relating to penicillin in NZ and the disputes that have arisen. Legal issues raised by penicillin are not fully explored; rather they have been used to provide a window into the patent-protected empire that can be built from a single discovery.

The Chemistry of Penicillins

What are Penicillins and How Do They Function?

When first isolated the structure of penicillin was uncertain. Beecham's Rolinson *et al*.[9] proposed the thiazolidine-oxazolone **2**, but it is now established[1] as the *β*-lactam **1** that carries a thiol ring and an amido side-chain.



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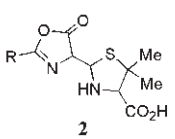

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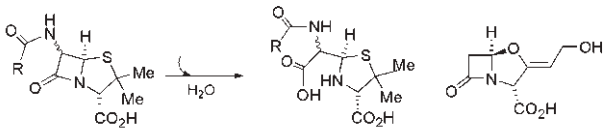
Bacterial cells have a high internal osmotic pressure and maintain shape integrity avoiding lysis (cell bursting) by having rigid cell walls. These walls are constantly being rebuilt as they are continuously degraded by enzymes in the surrounding medium. Penicillin prevents bacterial cells re-forming, causes lysis and is assisted by the high internal pressure.[1] Most penicillins affect only Gram-positive bacteria due to the composition of the cell wall. To function, penicillin needs to pass the wall and enter the plasma membrane that surrounds the central cytoplasm.[1] Lower density Gram-positive bacteria have walls *ca*. 25 nm thick that consist of cross-linked peptidoglycans and a thin layer of extracellular teichoic acids that offer little protection to drug penetration. Comparatively, Gram-negative cell walls are denser, only 2-3 nm thick, and have an outer lipid bilayer and periplasmic space that surrounds the peptidoglycan cell wall; this makes drug penetration difficult.[1]

β-Lactam antibiotics are able to diffuse through the outer membrane of Gram-negative bacteria whose porin channels (formed by proteins) allow the transport of such drugs. Once through the outer membrane, the drug must then diffuse through the periplasmic space that contains *β*-lactamases, which can inactivate the drug.[1] These *β*-lactamases, also produced by Gram-positive bacteria in their extracellular fluid, create *β*-lactam-resistant bacteria as they hydrolyze this ring to penicilloic acid (**3**), thus inactivating the penicillin (Scheme 1).[1,3] *β*-Lactamase inhibitors, such as clavulanic acid (**4**), are incorporated to overcome this.



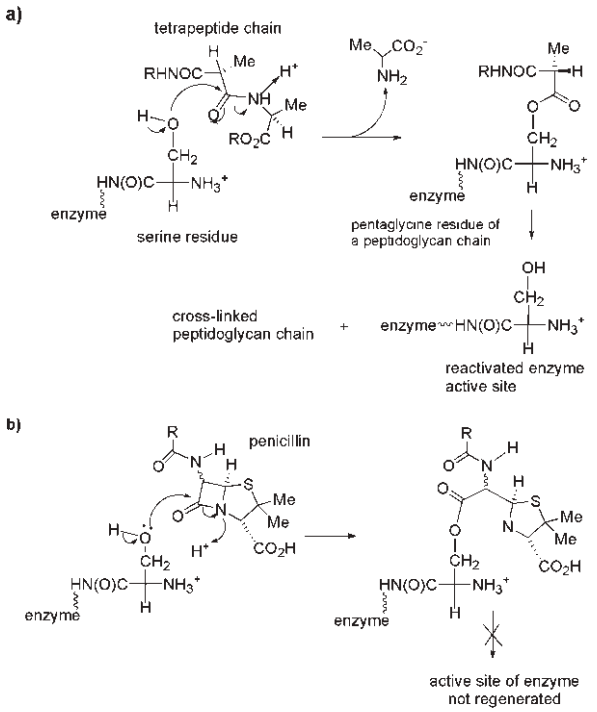
1, penicillin **3**, penicilloic acid **4**, clavulanic acid

Scheme 1. Inactivation of penicillin by β-lactamase.

Once at the plasma membrane, the penicillin binds to the transpeptidases (and other proteins) involved in cell wall synthesis and blocks their action from an interaction with its four-membered *β*-lactam ring.[1] It is thought that the glycopeptide transpeptidase needed for the final step of the cross-linking is inactivated due to the structural similarity of the amido carbonyl group adjacent to the terminus of the natural tetrapeptide chain with the carbonyl group of the *β*-lactam unit of penicillin.

The final step of cross-linking is believed to occur when a serine hydroxyl of the catalyzing enzyme (glycopeptide transpeptidase) attacks the carbonyl group next to the end of a tetrapeptide chain and displaces the terminal alanine (Scheme 2a). The enzyme is then displaced by the

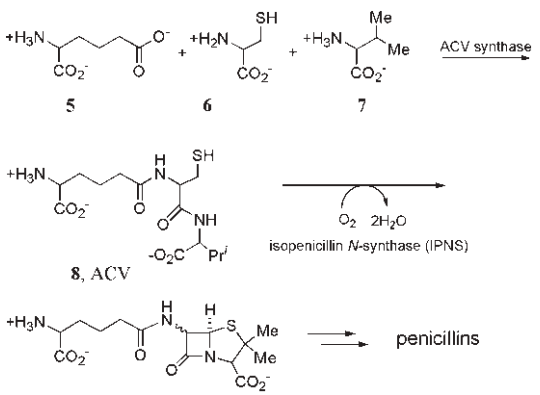
pentaglycine peptide bridge from another tetrapeptide chain, regenerating the enzyme (Scheme 2a).[1,10] However, in the presence of a highly reactive penicillin, this hydroxyl attacks the β-lactam carbonyl instead and forms a covalently bound acyl derivative that is slow to hydrolyze (Scheme 2b);[1,10] the 1,3-thiazolidine ring appears to prevent pentaglycine-induced enzyme-acyl bond cleavage. The active site of the enzyme is thus deactivated.[1]



Scheme 2. a) Normal cross-linking process in bacteria, b) penicillin intervention - see ref. 1

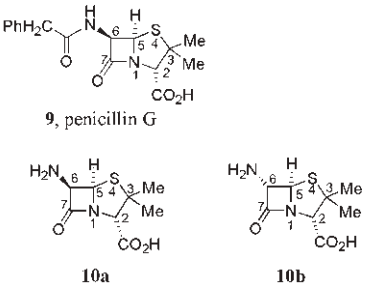
Synthesis of Penicillins

Penicillin biosynthesis in nature–Penicillins are secondary fungal metabolites, often isolated from *Penicillium chrysogenum*.[10,11] The fused lactam-thiazolidine rings are thought to be biosynthesized from L-*α*-aminoadipate (**5**), L-cysteine (**6**) and L-valine (**7**), These three peptides together (with the ACV synthase catalyst) form L-*δ*-(*α*-aminoadipoyl)-L-cysteinyl-D-valine (ACV, **8**), an acyclic tripeptide (Scheme 3). The bicyclic *β*-lactam is then formed from ACV by catalysis with isopenicillin *N*-synthase (IPNS), a non-heme Fe(II) enzyme. The side chain of *β*-lactam antibiotics formed from natural biosynthetic cyclization is L-aminoadipoyl and it can be epimerized to the D-form naturally.[10]



Scheme 3. Biosynthesis of penicillins.

Side-chain modification–*Penicillium chrysogenum* can produce more than one type of penicillin that differs only in the acyl side-chain of the *β*-lactam ring.[12] In the late 1940s, the identity of the side-chain resulting from the mould fermentation could be altered by adding requisite precursors to the brew, *e.g.* phenylacetic acid incorporates a benzylic group into the side-chain giving penicillin G (**9**).[12] Such modification continued throughout the 1940-50s but failed to provide[12] anything superior to penicillin G, until the discovery of 6-aminopenicillanic acid (**10**, 6-APA) in the late 1950s.



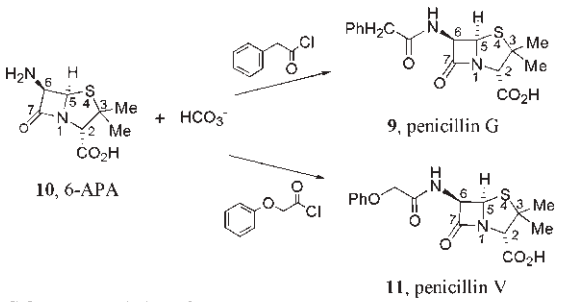
The discovery of 6-APA–Batchelor *et al*.[11] were the first to isolate, identify and appreciate the value of 6-APA (**10**). The molecule lacks the pendant acyl group of the fermentation products, and the UK patent application for it was made in 1957. While there is evidence that others[13] had previously stumbled across 6-APA, none had established its structure and assessed its possible use as a penicillin precursor.

Additionally, Batchelor's Beecham group discovered that **10** could be formed from penicillins by enzyme-catalysed hydrolysis in numerous micro-organism media with removal of the penicillin side-chain.[14] This was very important because the original isolation of **10** by fermentation was from a difficult process and in relatively poor yield.[4] The isolation of **10** from *Streptomyces lavendulae* and *Escherichia coli* (*E. coli*), as well as from *Penicillium chrysogenum*, was also demonstrated.[14] In March 1959, Beecham made patent application for the deacylation of phenoxymethylpenicillin [penicillin V (**11**) that they had also isolated] by *Streptomyces lavendulae*. Enzymatic hydrolysis in *Alcaligenes faecalis* also gives **10**, and small quantities have been isolated from *Aerobacter cloacae*, *Bacillus subtilis*, *Micrococcus lysodeikticus*, and *Myobacterium phlei* by a Bristol Laboratories group[15] who showed that both **9** and **11** reverted to **10** on hydrolysis.

Semi-synthetic variations–The discovery of side chain-free **10** was ground-breaking as it provided a penicillin directly usable as a precursor for semi-synthetic derivatives in a simple procedure without need for synthesis of the bicyclic lactam moiety.[3,4,11] For these reasons, **10** has been termed *the penicillin nucleus* that allowed research into this most important groups of antibiotics.[12] Prior to this 1957 discovery of **10**, **9** and **11** were the only penicillins of clinical relevance; following its discovery some twenty derivatives had entered clinical use by the end of 1970.[12]

In itself, **10** has antibiotic properties but its activity is much below than of the modified **9**,[11] which, unlike **10**, is not inactivated by penicillinase, a specific type of *β*-lactamase.[11] This increased potency, resistance and sta-

bility to enzymatic attack has allowed the spectrum of antibacterial activity to be broadened by systematically varying the side-chain through semi-synthetic modification employing **10**, and screening the products for desired traits.[10] Scheme 4 illustrates the ease by which *N*-acylations can be effected; Batchelor *et al*.[11] provided **9** and **11** with excess acid chlorides but they are hydrolyzed by *β*-lactamase.[11] A selection of synthetic analogues obtained from **10** and their properties appear in Table 1.

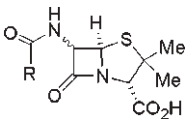


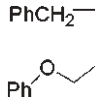
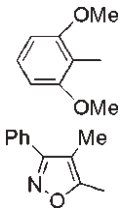
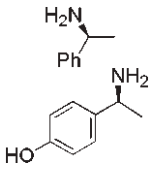
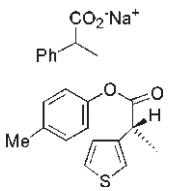
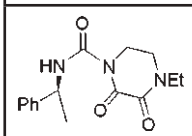
Scheme 4. Acylation of 6-APA.

Methicillin (**12**) was introduced in 1960 at a time when staphylococci had become seriously penicillin resistant.[5] It is effective against certain penicillin G-resistant bacteria[16] but its sensitivity to acid required it to be used subcutaneously rather than orally.[5] By 1961, strains of methicillin-resistant staphylococci had appeared![17] Oxacillin (**13**), also introduced in the early 1960s[4] is more active against penicillinase than methicillin and it exhibited high levels of protein binding in cell plasma.[18] It was followed by ampicillin (**14**; 1961), which had short term use against some Gram-negative bacteria until their resistance increased.[4] In 1964, amoxycillin (or amoxicillin; **15**) appeared from use of enantiomerically pure *α*-amino-*p*-hydroxyphenylacetic acid (**19**) with **10**.[19,20] All six stereo- and regioisomers of *α*-amino(hydroxyphenyl) acetylated **10** were tested, but the (6*R*)-amoxycillin (**15**) was the most effective.[21] It showed oral absorptions three times greater than its *m*-hydroxy regioisomer.[19,20]

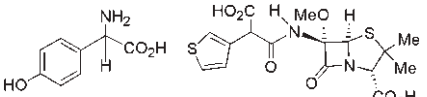
The greatly improved oral absorption of **15** *in vivo* required lower dosages than other penicillins[19,20] and made it the most widely prescribed antibiotic in clinical practice.[12] It is not known why its oral absorption is *ca*. twice that of ampicillin (**14**)[19,20,22] given that the structures differ only in a *p*-hydroxy substituent, but it is not due to differences in stability, in lipid or aqueous solubility, or pK_a values.[4] Moreover, the two penicillins behave similarly *in vitro*; only *in vivo* is there a difference.[4,23] A further advantage of amoxycillin in its reproducibility of oral absorption with little variation between patients.[4] The discovery of **15** led to worldwide patent disputes in no less than fourteen countries (see below) including NZ, which is usually free from disputes because of its small market. Carbenicillin (**16**), introduced in 1967, was the first *β*-lactam antibiotic effective against *Pseudodomonas aeruginosa*, a Gram-negative bacterium. The 1970 thiophene-containing ana-

Table 1. Different forms of penicillin - see ref. 9.



R	*Name*	*Category*	*Properties*
	Pen G **9** Pen V **11**	Narrow spectrum penicillinase-sensitive	Poor acid stability *β*-lactamase sensitive Good acid stability *β*-lactamase sensitive
	Methicillin **12** Oxacillin **13**	Narrow spectrum penicillinase-resistant	Both penicillinase resistant due to bulky side chains causing misalignment with *β*-lactamase active sites. High resistance to hydrolysis.
	Ampicillin **14** Amoxycillin **15**	Broad spectrum amino-penicillins	Orally active, good bioavailability. But, penicillinase sensitive. Active against Gram-negative bacteria
	Carbenicillin **16** Ticarcillin **17**	Broad spectrum anti-pseudo-monal	Increased penetration into porins. Can be administered intravenously.
	Piperacillin **18**	Extended spectrum	Increased activity against certain bacteria. Can be administered intravenously.

logue, ticarcillin (**17**),[12] was even more active against this bacterium.[4]

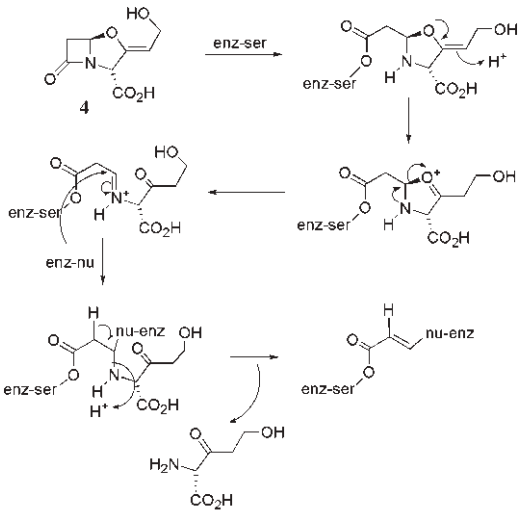


19, *R*:*S* **20**, temocillin

As use of penicillins increased, the resistance caused by *β*-lactamases continued to rise[4,24] demanding new *β*-lactamase-resistant penicillins – temocillin (**20**) became available in 1981. Stable against many *β*-lactamases including wide-spectrum derivatives, its clinical use has recently increased.[12]

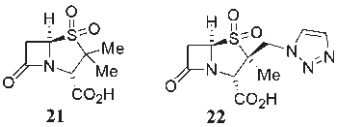
β-Lactamase Inhibitor—Clavulanic Acid (4)

In the 1950s, it was suggested that *β*-lactamase inhibitors could increase the efficacy of penicillins.[10] However, only with the discovery of clavulanic acid (**4**; Scheme 5) by the Beecham Group did a successful example exist.[25] Acid **4** is one of the most important *β*-lactamase inhibitors and remains in use thirty years after its discovery. It is a *β*-lactam enol ether from *Streptomyces clavuligerus* and it specifically targets serine-based *β*-lactamases[10] as a mechanism-based inhibitor. It is a suicide substrate of *β*-lactamase, thereby protecting the penicillin *β*-lactam from hydrolysis. The enol ether moiety in **4** weakens the *β*-lactam carbonyl bond and makes it more prone to attack by the active serine-OH than in penicillin (Scheme 5). Subsequent fragmentation and rearrangement gives an acylated enzyme that is not easily hydrolyzed and is thus deactivated.[10]



Scheme 5. Inactivation of β-lactamases.

In itself, **4** is not a strong enough antibiotic for sole use. Rather it is used in conjunction with other penicillins where it sacrifices itself and allows the penicillin to reach the plasma membrane. Commonly used is **4** with amoxycillin (**15**) – Augmentin™ – that has broad spectrum activity, is effective against a wide range of pathogens and makes a significant contribution to the fight against penicillin-resistant bacteria.[26,27] Augmentin™ is one of the most dominant anti-bacterial pharmaceuticals on the world market;[28] Timentin™, a combination of ticarcillin (**17**) and potassium clavulanate, is another.[27] Two other comparable *β*-lactamase inhibitors are sulbactam (**21**) and tazobactum (**22**), which are effective against serine-based *β*-lactamases.[10]



21 **22**

The Legal Position of Penicillins in NZ

A Short History

As mentioned earlier, Florey and Chain's group did not patent their pioneering penicillin-related work[5] but, in 1941, Chain indicated that their penicillin isolation should be patented with any accrued benefits put to further research.[29] Other members of the group, including Florey, regarded profiting from discoveries as unethical, a view common to academia in that era; patenting rather than publishing was looked upon unkindly.[3,5] This was the case when Moyer, a US collaborator with Florey, later tried to patent his developments; animosity remained between the associates for years.[3]

It could be that the Oxford work would have failed patent criteria as the 1941 *Lancet*[30] publication equated to public disclosure thereby removing novelty from the discovery.[5] Moreover, patents for compounds alone were not granted in most countries in 1941,[31] and the processes of manufacture and extraction were not new.[5] Pharmaceutical protection itself began in the UK in 1950 but not until 1955 in NZ.[31]

By 1955, however, Florey's position had changed and he much regretted having no patent for the penicillin extraction process.[5] This was not for personal reasons but because of the Anglo-American fight over penicillin ownership that the lack of a patent caused; some accused the US of stealing penicillin from Britain. When the US joined WWII in 1941, British researchers freely shared their penicillin results with the allies who subsequently transferred the research to the commercial interests of Merck, Squibb and Pfizer.[5] Penicillin was then mass produced by these companies using a *deep culture* process that was patented.[3] British producers used this (included the Ministry of Supply who had manufactured during the war) and a formal licence fee and royalties were expected.[5] An inquiry by the US Carnegie Institution found that no British firms had actually paid royalties but they had been charged for the know-how of the deep culture process.[5]

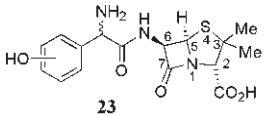
In today's world patenting by academia is common,[32] as evidenced by the approach taken with the anti-bacterial cephalosporins (ring-fused *β*-lactams, not dealt with here), discovered in the mid-1950s in another Oxford-led project. The patents for these [under the 1949 Patents Act (UK) that provided patents for substances] had provided the National Research Development Corporation, on behalf of Oxford University, substantially over £100 M by the late 1970s.[5]

Some of the Beecham Penicillin Patents

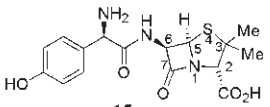
As well as the original patents for the isolation of **10**[33] and its acylation,[34] Beecham have been diligent and expedient in protecting the spin-off inventions and synthetic derivatives from **10**. A simple search under the Intellectual Property of NZ (IPONZ) for *penicillin* and *Beecham* provides eighteen different patents.[29]

A patent that covered an extensive class of *α*-amino acid-derived penicillins comprising various aminoacyl substituted **10** (*the amino patent*) was registered in 1959.[35] Because many *α*-amino acids are chiral, the patent included the optically active (*R*/*S*) forms as well as the racemic mixture. A *patent of addition*[36] was made four years later for *α*-amino(phenyl)penicillin, which was produced from racemic *α*-phenylglycine. Separation of the diastereoisomers led to (*R*)-*α*-amino-*α*-phenylpenicillin, which became known as ampicillin (**14**).[37]

In 1962, a further patent of addition was included in the UK[38] (but not NZ) for the preparation of all three regioisomeric phenol derivatives/variants of *α*-amino-*α*-phenylpenicillins (**23**) from the corresponding *o*-, *m*- and *p*-hydroxyphenyl-*α*-amino acids; three pairs of epimers (diastereoisomers) ensued as a result of using the racemic aminoacids. This patent is known as the OMP patent as it claimed all three epimeric pairs; amoxycillin (**15**) is the (*R*)-*α*-amino-*p*-hydroxyphenyl isomer. The specification of this patent also divulged results from tests of the (*R*)- and (*S*)-*α*-amino-*m*- and -*p*-substituted forms in mice using oral and subcutaneous administration. The results showed the compounds to be more active than ampicillin (**14**) against two Gram-negative bacteria, with the *m*-isomers the most potent.



23



15

In 1969, Beecham filed for a patent for amoxycillin (**15**) in NZ.[21] It was referred to in the specification as *a development of our [Beecham's] British patent No 978178* (the OMP patent). To form the pure (*R*)-*α*-amino epimer, **15** was made from enantiomerically pure *α*-amino-*p*-hydroxyphenylacetic acid and 6-APA (**10**; *cf*. Scheme 4).

Beecham's subsequent discoveries on the use of naturally occurring *β*-lactamase inhibitors in conjunction with the semi-synthetic derivatives of penicillin have also been attentively patented. In 1984, a combination of **15** with **4** was introduced and Beecham gained multiple NZ patents covering different processes for the preparation of **4**, its salts, and its use with penicillins, such as amoxycillin. Beecham subsequently patented[39] different compositions of amoxycillin with clavulanic acid (**4**) and has continued to patent methods of producing salts of acid **4**; the IPONZ database lists twenty different patents for *Beecham* and *clavulanic acid*.[29] Of all the Beecham penicillin-related patents, the most controversial in NZ is that for amoxycillin.

The Amoxycillin Case

The Bristol-Myers Company was not pleased with the world-wide amoxycillin applications that extended Beecham's property rights for the compound. In 1969, the NZ amoxycillin patent was disputed on the grounds of novelty and obviousness (lack of inventive step) because of the OMP patent filed in the UK in 1962 and subsequently published in NZ. The UK OMP patent ran from 1962–1976 and the amoxycillin patent from 1968–1982, thus extending protection by six years. OMP was not patented in NZ but amoxycillin was covered, to a point, by the 1959 amino patent (1959–1973 protection). The amoxycillin patent in suit would extend protection by ten years to 1983.

By the time the case reached Justice Cooke[40] (NZ Court of Appeal) corresponding disputes had been heard in thirteen other jurisdictions, but only in NZ and Australia was the protection that Beecham sought extended beyond oral use.[20] The claim was for amoxycillin itself and not just its oral use. This fact did not prevent Justice Cooke from finding that there was novelty and that the invention was not obvious; nor did the appearance of amoxycillin in the OMP patent interfere. However, because the inventive step *was found to lie in the exceptional oral absorption of amoxycillin*, the scope of the patent was required to be limited as such.

Novelty (prior publication)–Under the Patents Act 1953,[41] patent applications can be opposed if the claims have been published previously. Bristol-Myers argued that the OMP patent was prior publication of amoxycillin. The issue was whether it published amoxycillin *so far as claimed in any claim of the complete specification*.[20] The OMP patent clearly included amoxycillin, as it covered both *R*/*S*-*α*-amino epimers of all three (*o*-, *m*-, *p*-hydroxyphenyl) regioisomers of *α*-amino(hydroxyphenyl)penicillin (**23**). Furthermore, the OMP patent stated that the isomers could be prepared and isolated according to the methods described in the amino patent, although it did not give a full and explicit method for preparing the (*R*)-*α*-amino-*p*-hydroxy isomer in its optically pure form. Specifically, it failed to disclose how the side-chain acid was initially resolved prior to reaction with **10**. However, it was agreed by both parties that a normally skilled chemist would be able to do this without any invention, though some trial and error would be required.[20]

In making its decision, the Court of Appeal rejected a literal approach to the prior publication test *preferring* a more direct approach as to whether the invention claimed had been *published* previously in NZ, in relation to semi-synthetic chemical compounds: *If such a compound has not been made before, its properties often cannot be predicted with confidence; and where that is the case [as the Court found] one cannot consider that the invention claimed can fairly or accurately be described as published, even if a skilled chemist would realize that to make the compound by routine means would be practicable. A making of the compound and a discovery of its properties is necessary before the invention has occurred and can be published*.[20] Thus, whether or not the OMP gave explicit instructions as to how to make the (*R*)-*α*-amino-*p*-hydroxy isomer was not the decisive factor. Rather, novelty was found because the isomeric form had not actually been made and tested before, even though disclosed. If a chemical compound has not been made, it cannot be held to be known or used just because it is predicted as a theoretically possible compound.[20,42]

This conclusion leads to the situation that *there can be no invention in particular penicillins before they have been actually produced, so as to enable their therapeutic*

characteristics to be ascertained.[20] Bristol-Myers further contended that Beecham had already made amoxycillin before they applied for the OMP patent as it was one of the isomers in the *p*-hydroxy mixture. This argument was rejected, as the compound had not been separately made or isolated.[20]

Finding novelty in an epimer apart from its existence in a pair of diastereoisomers is somewhat contentious. However, because a pair of diastereoisomers have different chemical and biochemical properties from each other and from their (*R*/*S*) mixture, the Court of Appeal's finding is understandable and supportable on a scientific level. That the court found that the invention was not obvious is more controversial.

Non-obviousness–In addition to novelty, claimed inventions also must be either non-obvious or involve an inventive step. Non-obviousness differs from novelty in that it is qualitative rather than quantitative. The non-obviousness standard is used to distinguish patent-worthy inventions from routine or slight advances to the prior art.[43] If there is no inventive step, relative to that published or used before the priority date of an application, an application can be opposed.[41]

There are several good reasons for the conclusion to the claim that amoxycillin as a compound was obvious, and lacking in any inventive step.[44] Firstly, the (*R*)-*α*-amino-*p*-hydroxyphenyl isomer was already divulged in the OMP patent. Secondly, its possible clinical use was apparent given that the OMP patent showed that the three epimeric pairs had desirable properties against Gram-negative bacteria, and that *p*- and *m*-hydroxy (*R*/*S*) mixtures showed greater activities than their predecessor, ampicillin.[20] Thirdly, counsel for Beecham made it clear that they were not contending whether the actual making of amoxycillin involved an inventive step.[20] Fourthly, it is commonly known that a pure isomer is likely more efficient than its racemic mixture, and the OMP patent had made this clear with respect to α-amino(hydroxyphenyl)penicillin.[20]

The Court of Appeal found that it was obvious to try the (*R*)-*α*-amino-*p*-isomer in the search for generally better penicillins, and that this isomer had not yet been singularly made and tested. This was supported as both Beecham and Bristol-Myers independently tested it.[20] However, the Court of Appeal came to the conclusion that there was an inventive step because the unexpected higher oral absorption of amoxycillin over ampicillin and the other isomers of α-amino(hydroxyphenyl)penicillin.[20] The OMP patent had expounded no such finding, nor had it inferred it. The Court stated that:[20]

> The search for medical advance is to be encouraged. It can be long, expensive and fruitless. The pursuit of one of a number - perhaps many - obvious lines of research may produce a signal or particularly valuable discovery. In deciding on patentability it would seem to us regrettable, and not in accord with a primary purpose of patent law, to have to rule this out automatically in the name of obviousness. We think that the pursuit of an obvious line of research, in the synthesising and testing of a new chemical compound, may be held to culminate in an invention which is not obvious and does involve an inventive step, if a sufficiently distinctive advantage is discovered. It is a question of degree ...

The finding of non-obviousness in this case is somewhat dubious. It was held that the (*R*)-*α*-amino-*p*-isomer was obvious to try as a possible anti-bacterial agent and that no new methodology was required to create the isomer. Thus, the finding does not seem to stand on a scientific basis rather than on the end use of the claimed invention. Indeed, the finding of non-obviousness was influenced by amoxycillin being commercially very successful in NZ, which implies that the advantage given by amoxycillin over ampicillin entitles its inventor to protection.[20]

Because patents limit market competition, a founding principle to their grant is that they encourage innovation, which would otherwise not occur.[45] A further justification for the patent system is that it encourages inventors to divulge the information behind their inventions, rather than keeping trade secrets hindering the advance of science and technology.[31] The patent system is not intended to reward work;[46] such a role is ancillary. If the (*R*)-*α*-amino-*p*-isomer was an obvious compound to try, such that it did not involve much risk, and no new scientific information was obtained (no unknown compound or process was created), the finding of non-obviousness appears to go against the purposes of the patent system,[46] and purely rewards work. Thus, holding non-obviousness cannot be supported either scientifically or by the purposes of the patent system. There seems no good reason why Beecham were given further patent protection for a compound that they already had property rights for in their OMP patent, merely because they discovered properties previously unknown to them. That the properties were unexpected does not make the claimed invention fall into the purposes of the patent system, nor is it a very good or precise legal test.

The scope of the patent–A redeeming feature of this case is that the Court narrowed the scope of the claim for the invention. The 1953 Patents Act requires that every complete specification *[s]hall end with a claim or claims defining the scope of the invention claimed*.[20,41] Bristol-Myers argued that the patent claim should be limited to the oral use of amoxycillin - as in other jurisdictions such as the UK, where it had been limited to a pharmaceutical composition designed for oral administration.[20]

It was stated that *what is of direct concern ... is that a patent should not be granted and the public domain not restricted except to the legitimate extent of an invention. To put it tritely, a man should not have a patent for more than he has invented*.[20] The finding was made that *it [w]as artificial to try to define the scope of the invention ... without any linking or reference to the high oral absorbability in man which, in combination with high anti-bacterial activity, is said to give the compound its unique advantage and which ... enables the objection of obviousness and want of inventive step to be answered. Accordingly, ... any patent should be limited to the use of the compound in a composition for oral administration to human beings*.[20]

Ownership in Small Variations?

Pharmaceutical companies commonly attempt to extend their patent rights over essentially the same compounds. This is often done by making small variations to existing drugs, or by creating new composition or dosage claims.

This *evergreening* has been said to occur (rather sceptically) by finely tuned planning before an application is made for the first patent.[47] Accordingly, information is split into multiple patents with applications staggered to lengthen the overall protection term.[47] Whether these variations are justified or not is beyond present scope, but the practice is prevalent with Beecham and their penicillins.

Amoxycillin/clavulanic acid composites–Beecham has had multiple patents for clavulanic acid (**4**) and its compositions. The IPONZ website shows four different such patents, one of which is still in force. In 2001, DSM NV sought to have one of these revoked for lack of novelty or for obviousness.[48] The patent was for a different weight ratio of amoxycillin (**15**) to **4** and a means of coating the tablet not previously published; it was held novel and not clearly obvious. DSM NV additionally challenged another **15**/**4** patent[49] with a different weight ratio that specifically targeted pediatric use. Again, it was found that obviousness had not been made out.

Should such patents be granted? Companies do invest large sums of money to formulate new compositions and usually these are more efficient or target a specific use. However, as patents are not a reward for work or investment, but for new information divulged to society, it is questionable whether the information obtained from new formulations are worthy of patent rights. Scientific research is directed to the discovery of previously unknown information; the presence of some new information behind an incremental invention should not automatically import patentability. Society should bear the costs associated with limited competition only if the information divulged in the patent is worthy and would otherwise not have been disclosed.

Interestingly, the US Federal Circuit is sceptical of strategies that prolong patent protection.[50] Recently, it invalidated a subsequently issued patent based on the parent[51] for Augmentin™ on the grounds of *double patenting*.[52] Augmentin patent protection was to lapse in the US in 2002. However, Beecham attempted to patent (temporarily succeeding) *new found* properties of Augmentin™ that extended protection until 2017. It was alleged that the work in question had been done in the 1970s.[53] In a summary judgement,[54] the Court held that the later application appeared to be a rewording of the previous patent.[52,55] And so Novartis brought an antitrust[56] action against Beecham in 2004 and Beecham agreed to pay $US 92 M to direct and indirect purchasers, and third-party payers. Augmentin™ had global sales of > $US 2 billion at that time.[57]

Ampicillin trihydrate–Another interesting NZ case was an attempt by Bristol-Myers to patent ampicillin (**14**) trihydrate following the lapse of the Beecham monohydrate patent.[44] Beecham opposed the application arguing that it was not new and obvious. The decision turned on whether ampicillin monohydrate had ever existed. Beecham denied that it had, argued that it was unlikely that they ever had penicillin monohydrate, and that at the time of their ampicillin patent, technology was not available to fully prove this. Evidence showed that the trihydrate was obtained when the method in the original patent was applied at the time of the dispute. Bristol-Myers was not able to prove that Beecham had ever made ampicillin monohydrate or that the conditions of the experiment had changed to explain why the trihydrate was now formed. The case was decided in Beecham's favour.

Whether ampicillin trihydrate had been previously published or not should not determine novelty. The trihydrate is the most stable form, but the active component is **14** itself. Furthermore, as the trihydrate is the more stable form, were the monohydrate actually made, it would have taken up moisture and transformed into the trihydrate. Controlling the moisture content of the environment to maintain the monohydrate would be impractical. Consequently, the inference that the different content of water could make a new invention is flawed.

The Beecham Penicillin Empire

Beecham's tight grasp on penicillin is not surprising given they owned the patent for 6-APA (**10**) that began the evolution of semi-synthetic penicillins. A flaw of the patent system is that the 20 year protection given to encourage innovation can, in fact, stifle it by preventing other groups from working with the invention and creating spin-offs. It explains why Beecham continues to dominate the penicillin market with new semi-synthetic variants and new dosage forms. Amoxycillin, first patented in NZ in 1969, remains in the patent system. Over this 40 year period, Beecham has had some 23 patents relating to it and they attempted to get the NZ term extended.[58] This was opposed by Pacific Pharmaceuticals Ltd.,[59] but the outcome is not clear as the IPONZ cases were not substantive.[60]

Beecham did extend their original NZ patent for clavulanic acid (**4**) by eight years as represented *lost years* between the initial application and patent approval.[26] In their extension application, the relatively high notional royalty rate of 17.5% was deemed reasonable because of the merit of the invention. The invention was considered an *exceptional case* due its great public benefit and that it was discovered through many difficulties. Equivalent patents were also extended in Australia, South Africa and Ireland.

Augmentin™ was ranked 4th in global anti-bacterial sales for 2007,[28] reaping £530 million,[61] even though the individual patents for amoxycillin and clavulanic acid, and the initial composition, have lapsed. The NZ pharmaceutical market is difficult to compare with others because Pharmac's decision *to subsidize or not* has a major impact. However, Augmentin™ remains the only amoxycillin/clavulanic acid composition subsidised by Pharmac,[62] despite generic versions on the global market.

Concluding Remarks

The discovery of penicillin and the nature of its nucleus are among the most important made by mankind.[63] Penicillin-related pharmaceuticals are in daily use and have saved many lives. Determining exactly how they function *in vivo* took time but assisted research into combating β-lactam-resistant bacteria. That much study is still conducted on penicillins measures their importance to society, and their continued patent protection demonstrates

their unremitting monetary value to the pharmaceutical industry.

The empire that Beecham has built over their patent of 6-APA (**10**) is likely a model that others would wish to follow. Fifty years after their original patent, the Group continues to dominate the penicillin-related market and the intellectual property protection for such pharmaceuticals in NZ. Since the initial discoveries of **10** and **4**, it is arguable that no *new* inventions have been made, but that Beecham is riding the waves of its previous ingenuity. We have not sought to resolve whether the aims of patent law are met by allowing patents for such *inventions*, but we suggest that perhaps they are not and that companies (such as Beecham) are gaining patent protection for minor variations that are scientifically routine and obvious.

No absolute conclusion can be drawn, but with the low inventive threshold that currently pertains, Beecham is likely to have patent protection for penicillin-related pharmaceuticals for some time to come. This is particularly true since SmithKline Beecham and Glaxo Wellcome merged in 2000 creating GlaxoSmithKline (SmithKline Beckman and Beecham merged in 1989,[64] and Glaxo and Wellcome in 1995[65]). It is now the largest company in the UK[66] and the largest pharmaceutical company worldwide.[67]

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Dates of Note

Stanislao ***Cannizzaro*** was born on 13 July 1826, while the following day marks the 75th anniversary of the death of *Marie* ***Curie*** and the 102nd of Sir *Wiliam* ***Perkin***. 1973 Nobel Laureate in Chemistry Sir *Geoffrey* ***Wilkinson*** (with Ernst Fischer) was born on July 14, 1921 and *Emil* ***Fischer*** passed away 90 years ago on the 15th.

July 15 marks the 140th anniversary of patenting margarine in France by *Hippolyte Mège* ***Mouriés***. He won the contest held by Emperor Napoleon III to find a substitute for butter used by the French Navy. His formula included a fatty component that mixed to a pearly lustre and so he named his product after the Greek for pearl - *margaritari*. His margarine was manufactured from tallow and it was not until Boudet patented a process for emulsifying it with skimmed milk and water (1872) that it became sufficiently palatable to be a commercial success.

July 17 is the 182nd anniversary of Sir *Frederick (Augustus)* ***Abel***'s birth. He, with Sir James Dewar, invented cordite 120 years ago in 1889. The 20th is the 40th anniversary of Neil Armstrong's first walk on the moon.

Rosalind ***Franklin***, who contributed to the discovery of the structure of DNA, was born on July 25, 1920. This day also marks the 50th anniversary of the first hovercraft crossing of the English Channel between Calais and Dover by SR.N1. *Raoul Pierre* ***Pictet***, a pioneer of cryogenics, died 80 years ago on July 27; *John* ***Dalton*** preceded him some 85 years earlier (1844). *Francis* ***Crick*** died 5 years ago on July 28 and *Dorothy* ***Hodgkin*** 15 years ago on the 29th.

Sir *George Thomas* ***Beilby***, the Scottish industrialist who developed the process for manufacturing potassium cyanide (widely used to extract gold from low-grade ore) died on August 1, 1924. It is also the day 235 years ago (1774) that Joseph Priestley identified a gas which he called *dephlogisticated air* – oxygen.

Feodor ***Lynen***, the 1964 Nobel Laureate (with Bloch) in Physiology or Medicine for his research concerning the mechanism and regulation of the cholesterol and fatty acid metabolism, died on August 8, 1979, while Sir *Edward* ***Frankland***, famed for his proposals on the chemical bond and valence, died 110 years ago on Aug. 9. The first use of the radio distress call ***SOS*** was made by the liner *S.S. Arapahoe* on Aug. 11, 1909.

Sir *Ernst Boris* ***Chain***, the German-born British biochemist who shared the 1945 Nobel Prize for Physiology or Medicine (with Fleming and Florey) for work on penicillin, died 30 years ago on August 12. This day also mark the 13th anniversary of NZ becoming the second country to establish a national DNA databank when the enabling Act took effect. August 14 marks the 15th anniversary of the death of *Linus* ***Pauling***

Sune K. ***Bergstrom***, the Swedish biochemist who shared the 1982 Nobel Prize (with Samuelsson and Vane) for Physiology or Medicine for the isolation, identification, and analysis of prostaglandins and related biologically active substances, died 5 years ago on Aug. 15. *Robert* ***Bunsen*** died on Aug 16, 1899. August 18 is the 15th anniversary of *Richard* ***Synge***'s death. He was a British biochemist who shared the 1952 Chemistry Nobel Prize (with Martin) for the development of partition chromatography, notably paper chromatography.

Franz C. ***Schmelkes*** discovered azochloramid (*N*1,*N*2-dichloro-1,2-diazenedicarboximidamide), which is used to sterilize wounds and burns. He was born 110 years ago on Aug19, while *Jöns Jacob* ***Berzelius*** was born 210 years ago on Aug 20, 1799.

Aug. 27 marks the 150th anniversary of the drilling of the first oil well by Colonel *Edwin L.* ***Drake*** (in the US near Titusville, Pennsylvania) and 20 years later Aug. 27, 1879, was born *Carl* ***Bosch*** (of Haber-Bosch fame). Aug. 30 is the 125th anniversary of the birth of *Theodor H.E.* ***Svedberg***, the Swedish chemist who won the 1926 Nobel Prize for Chemistry for his work on colloids. Sir *Ernest* ***Rutherford*** was born on August 30, 1871.

The first use of chemotherapy was 100 years ago on Aug 31 by Nobelist *Paul* ***Ehrlich***. Some time before, he had given his assistant, Sahachiro Hata, two organic arsenic compounds to test as a treatment for syphilis caused by *Treponema pallidum*. Hata became the first to discover how to infect rabbits to produce syphilis. After many careful experiments, success was gained with *Preparation 606* (the 606th chemical devised by Ehrlich's team). On 31 Aug 1909, Ehrlich watched Hata inject 606 into a rabbit with syphilitic ulcers that were cured within a month. Thus, syphilis was the first disease caused by a microorganism to be cured with a specific drug.

Paul ***Vieille***, who invented smokless powder (Poudre B,) was born on Sep. 1, 1854. Austrian *Fritz* ***Preg*** pioneered organic microanalysis and received the 1923 Nobel Prize for it; he was born on 3 Sep. 1869. Australian-born British chemist Sir *John* ***Cornforth***, who shared the 1975 Nobel Prize for Chemistry (with Prelog) for his work on the stereochemistry of enzyme-catalyzed reactions, is 92 on Sept 6. *August* ***Kekulé*** was born on Sept. 7th 1829, 180 years ago. Sept. 10th marks the 10th anniversary of the death of *Waldo* ***Semon*** who invented plasticized PVC in 1926, and 25 years to the day when DNA fingerprinting was discovered (Leicester, England) by *Alec* ***Jeffreys***.

Thomas ***Graham*** (of Graham's Law fame) died on Sept 14, 1869, the day 50 years ago that the first space probe, Soviet *Luna 2*, struck the moon. The use cocaine as a local anaesthetic to immobilize a patient's eye for surgery was by *Carl* ***Koller*** 125 years ago on Sept. 16. His success initiated the modern era of local anesthesia, with cocaine also quickly adopted for nose and throat surgery and for dentistry; Lavoisier observed the generation of O_2 on heating HgO the same day in 1874.

Sept. 20 marks the 150th anniversary of the electric range patent by *George B.* ***Simpson*** of Washington DC. The 23rd is 80 years since the death of little recognised *Richard* ***Zsigmondy***, who was awarded the Nobel Prize for Chemistry in 1925 for his demonstration of the heterogeneous nature of colloid solutions and for the methods he used, which have since become fundamental in modern colloid chemistry.

Sept. 24th is the 200th anniversary of the birth of *Robert John* ***Kane***, the Irish chemist who was the first to propose the existence of the ethyl radical. He was Professor of Chemistry at Dublin's Apothecaries' Hall. *Paul* ***Scherrer***, who collaborated with Debye on the development of a method of X-ray diffraction (the Debye-Scherrer method) to identify materials that do not readily form large, perfect crystals, died on Sept. 25, 1969. Sept. 30 is the 70th birthday of *Jean-Marie* ***Lehn***, 1987 Nobel laureate and recent visitor to NZ.

Oct. 5 is the 5th anniversary of the death of NZ Nobel Laureate *Maurice* ***Wilkins***, while the 7th is the 70 birthday of Sir *Harry* ***Kroto***, another recent visitor to NZ. The day is also the 50th anniversary of the dark far side of the Moon being photographed for the first time.

Oct. 9 marks the 50th anniversary of the death of Sir *Henry* ***Tizard***. His work on aircraft fuels ultimately led to the octane rating system that expresses the anti-knocking characteristics of the fuel. It is also the 130th anniversary of *Max von* ***Laue***'s birth.

Henry ***Cavendish***, the English physicist and chemist, was born in Nice on Oct. 10, 1731, while Oct. 11 is the 125 anniversary of *Friedrich* ***Bergius***'s birth. He is the German chemist who converted coal dust and hydrogen directly into gasoline and lubricating oils without isolating intermediate products in 1921. The day also marks the 120th anniversary of *James Prescott* ***Joule***'s (Joule's Law) death.

Paul Hermann ***Müller***, the Swiss chemist who received the 1948 Nobel Prize for Physiology or Medicine for discovering the potent toxic effects on insects of DDT, died on Oct. 12, 1965. Oct. 13 marks the 125th anniversary of Greenwich being adopted as the universal meridian.

Alfred ***Nobel***'s first patent was granted on Oct. 14, 1863 while *Konrad* ***Bloch***, the German-born American biochemist who shared the 1964 Nobel Prize for Physiology or Medicine (with Lynen) for discoveries concerning the natural synthesis of cholesterol and of fatty acids, died on Oct 15, 2000.

Conference Calendar

18th International Symposium on Olefin Metathesis and related chemistry, Leipzig, Germany, 2-7 August.

Further details available at the website:
http://www.isom18.com/

AIMECS09, 7th AFMC International Medicinal Chemistry Congress, Cairns, Australia, 23-27 August.

Further details available at the website:
http://www.AIMECS09.org/

27th ISSY, Pasteur's Legacy, yeasts for health and biotechnologies, Paris, France 26-29 August.

Further details available at the website:
http://www.pasteur.fr/issy27

7 ICfE 2009, 7th International Conference on f-Elements, Cologne, Germany, 23-27 August.

Further details available at the website:
http://www.icfe.de/

13th BMOS, Brazilian Meeting on Organic Synthesis, Sao Pedero, Brazil, 31st August – 4 September.

Further details available at the website:
http://www.bmos13.ufscar.br/

ESERA, European Science Education Research Association, Conference, Istanbul, Turkey, 31st August – 4 September.

Further details available at the website:
http://www.esera2009.org/

13th International Conference on the Application of Density Functional Theory in Chemistry and Physics, Lyon, France, 31 August-4 September.

Further details available at the website:
http://www.dft09.org/

EuroAnalysis 2009, The Impact of Analytical Chemistry on Quality of Life, Innsbruck, Austria, 6-10 September.

Further details available at the website:
http://www.euroanalysis2009.at/

The 12th European Symposium on Organic Reactivity, Haifa, Israel, 6-11 September.

Further details available at the website:
http://www.congress.co.il/esor09/

QUITEL 2009, XXXV Congress of Theoretical Chemists of Latin Expression, San Andres, Colombia, 18-22 September.

Further details available at the website:
http://www.quitel.org/

ICCE 2009, International Conference on Chemical Engineering, Amsterdam, The Netherlands, 23-25 September.

Further details available at the website:
http://www.waset.org/wcset09/amsterdam/icce/

5th Black Sea Basin Conference on Analytical Chemistry, Fatsa-Ordu, Turkey, 23-26 September.

Further details available at the website:
http://www.5bbcac.org

ISABC10, 10th International Symposium on Applied Bioinorganic Chemistry, Debrecen, Hungary, 25-28 September.

Further details available at the website: http://www.isabc10.unideb.hu/

10th International Conference on Frontiers of polymers and advanced materials, Santiago, Chile, 28 September-2 October.

Further details available at the website:
http://200.89.74.77/

FACSS 2009, The Federation of Analytical Chemistry and Spectroscopy Societies Annual Conference, Louisville, Kentucky, USA, 18-22 October.

Further details available at the website:
http://facss.org/

ICCMSE 2009, Seventh International Conference of Computation Methods in Sciences and Engineering, Rhodes, Greece, 29 September- 4 October.

Further details available at the website:
http://www.iccmse.org/index.htm

BIT's 7th Annual Congress of International Drug Discovery Science and Technology, Shanghai, China, 22-25 October.

Further details available at the website:
http://www.iddst.com

ICCE 2009, 4th International Congress of Chemistry and Environment, Guilin, Guangxi, China, 7-9 November.

Further details available at the website:
http://www.chemenviron.org/environ/icce_2009/index.htm

22CRC 22nd Conference of Residue Chemists, Sydney, Australia, 9-12 November 2009.

Further details available at the website:
http://www.crcaustralia.com.au/

PIPOC 2009, Palm Oil Congress, balancing ecologics with economics, Kuala Lumpur, Malaysia, 9-12 November.

Further details available at the website:
http://www.mpob.gov.my/

6th Singapore International Chemical Conference, Chemical Synthesis: Creativity and Applications, Singapore, 15-18 December.

Further details available at the website:
http://sicc6.org/

11th Frank Warren Conference, covering all branches of organic chemistry, Pietermaritzburg, South Africa, 17-21 January, 2010.

Further details available at the website:
http://chemweb.unp.ac.za/FW2010/

ICCC39, 39th International Conference on Coordination Chemistry, Adelaide, Australia, 25-30 July 2010. ICCC39 will encompass all aspects of coordination chemistry through plenary, keynote and section lectures and poster presentations.

Further details available at the website:
http://iccc2010.eventplanners.com.au/

Grants and Scholarships

Grants, scholarships and funding currently available for your application.

International Conference Fund

This fund is provided by the Minister of Research, Science and Technology and administered by the Royal Society of New Zealand. It is to assist organizations and institutions to host major international conferences in New Zealand.

There is no closing date for applications.

For further information see the website:
http://www.rsnz.org/funding/int_conf/

Seed Funding

The Royal Society of New Zealand has a limited amount of funding to assist organizations setting up meetings, workshops or symposia.

There is no closing date for applications.

For further information see the website:
http://www.rsnz.org/funding/int_conf/

Conference Assistance Programme

This programme is to provide assistance for bidding to host an international conference in New Zealand. This can include discounted airfares to travel to present a bid, help to write bid documents and accompanying marketing material, as well as other assistance.

For further details see the website:
http://www.conventionsnz.com/cap.aspx

Foundation of Research, Science and Technology

The Foundation of Research, Science and Technology has a number of on-demand schemes that provides funding to enable businesses to develop new research and development projects. There are a number of different options available.

The following website has a table with how often these are considered and further details about the various schemes.

http://www.frst.govt.nz/investframe/process/ondemand

Bio-Market Development funding

This fund offers eligible biotechnology businesses up to $50,000 (Ex GST) for developing trans-Tasman partnerships that aim to open up new markets beyond New Zealand and Australia.

For further details see the website:
www.nzte.govt.nz/find-funding-assistance/australia-new-zealand-biotechnology-partnership-fund/anzbp

The Escalator Service

This service provides assistance to any business or entrepreneur who needs to raise funds to expand, diversify or commercialise a new concept.

For further details see the website:
http://www.nzte.govt.nz/find-funding-assistance/pages/capital-raising-advice-and-assistance.aspx

Claude McCarthy Fellowship

This fellowship has four categories for graduates of science, medicine and literature from a New Zealand university. The first one provides for up to $5,000 for a graduate who is registered or enrolled for doctoral degree to travel overseas to present at a conference or do a short period of research towards their doctoral degree. Category B provides for up to $30,000 to enable a graduate whose normal occupation does not allow them to undertake research to carry out research at a New Zealand university. Category C provides for up to $40,000 for any university staff member who is a graduate, to carry out original research outside their organization. Category D provides for not more than $10,000 for any university staff member who is a graduate, to take leave to travel overseas to do up to three months research.

Closing date for applications is 1 August 2009.

For further details see the website:
http://www.nzvcc.ac.nz/scholarships/claudemccarthy

Woolf Fisher Scholarships

This scholarship is for three or four years of postgraduate research leading to a doctoral degree or equivalent at the University of Cambridge or the University of Oxford.

A Woolf Fisher Scholar receives a maintenance allowance of £12,000 per year as well as an approved college fee, university composition fee and an annual return economy airfare from London.

Closing date for applications is 1 August 2009.

For further details see the website:
http://www.nzvcc.ac.nz/scholarships/woolffisher

Kia Ora Foundation Travelling Scholarship

This scholarship is to provide funds for individuals to travel overseas to undertake scientific research essential to their postdoctoral work, (not conference attendance). Up to $20,000 is available for distribution.

Closing date for applications is 1 August 2009.

For further details see the website :
http://www.nzvcc.ac.nz/scholarships/kiaorascience

Rutherford PhD scholarships to Cambridge

These scholarships are for applicants undertaking full-time study towards a PhD at Cambridge University in pure or applied science. The Rutherford Scholars receive an allowance of approximately £10,500 for up to three years as well as university and college fees and one return airfare between New Zealand and the United Kingdom.

Closing date for applications is 1 August 2009.

For further details see the website :
http://www.royalsociety.org.nz/Site/rutherford/guidelines.aspx

R.H.T. Bates Postgraduate Scholarship

This scholarship is available to all graduates who are registered for a PhD in the physical sciences (physics, chemistry and mathematical and information sciences) and engineering. It is a single award of $5000.

Closing date for applications is 1 September 2009.

For further details see the website:
http://www.royalsociety.org.nz/Site/funding/MedalsAwards/awards/academy_awards/bates.aspx

Todd Foundation Postgraduate Scholarship in Energy Research

This scholarship is to support students undertaking doctoral research in the field of energy, which may have relevance and value to New Zealand.

Closing date for applications is 1 September 2009.

For further details see the website:
http://www.nzvcc.ac.nz/scholarships/toddenergy

Te Tipu Putaiao Fellowships

These fellowships are for students completing masters, doctorate or postdoctoral work in a science, engineering or technology discipline. Funding depends on the qualification ranging from $10,000 stipend for a masters to $61,000 for a post doctorate.

Closing date for applications is 2 September 2009.

For further details see the website:
http://www.frst.govt.nz/funding/students/TTP

New Zealand Science and Technology Postdoctoral Fellowship Scheme

These fellowships are for those with a doctoral degree. The fellowships are to carry out postdoctoral research. Funding is $61,000 per annum for up to three years and up to $30,000 per annum for research related costs.

Closing date for applications is 12pm, 3 September 2009.

For further details see the website:
http://www.frst.govt.nz/funding/students/postdoc

New Zealand Science and Technology Postdoctoral Bridge to Employment Scheme

This fellowship is to provide support for fellows to move into full-time employment with a New Zealand science and technology organization. It is for up to twelve months, 50% salary contribution with a maximum of $36,250(ex GST).

Closing date for applications is 12pm, 3 September 2009.

For further details see the website:
http://www.frst.govt.nz/funding/students/postdoc

The Todd Foundation Awards for Excellence

These awards are to support projects, which encourage the development of new concepts, technology or research, which will benefit New Zealand. They include the category of science and technology. A candidate must have a degree or equivalent. The value of the award depends on the nature of the research project.

Closing date for applications is 1 October 2009.

For further details see the website:
http://www.nzvcc.ac.nz/scholarships/toddexcellence

Wool Research Organisation of New Zealand Inc and New Zealand Wool Industry Charitable Trust Post Doctorate Fellowships

These fellowships are for holders of PhDs for study and research in topics related to wool including protein chemistry and process chemistry. Successful applicants receive a stipend of between $50,000-$65,000 per year for up to three years.

Applications close 31 October 2009.

For further details and the research topics given priority see the website:
http://www.meatandwoolnz.com/main.cfm?id=233

New Zealand Postgraduate Study Abroad Award

This award is available to postgraduate students enrolled in either Doctoral or Master's degree programmes at a New Zealand institution, whose research would benefit from up to six months of study or research overseas. The value of the award is up to $10,000 depending on the proposed project.

Closing date for application is 1 November 2009.

For further details see the website:
http://www.newzealandeducated.com/int/en/institutions_courses/scholarships/outgoing/new_zealand_postgraduate_study_abroad_award

Post Graduate Field Research Awards

This award is for a maximum of $5,000 for a Doctoral student and $3,500 for a Masters student to carry out field research in developing countries for at least four weeks.

Closing date for applications is November 2009.

For further details see the website:
http://www.nzaid.govt.nz/scholarships/postgraduate-awards.html

Science Scene

Prime Minister gets a Chief Science Advisor

John Key has appointed Prof. Peter Gluckman as his Chief Science Advisor. This is the first time the Prime Minister has had a Chief Science Advisor.

The role is a part-time one so Prof. Gluckman will continue, in a reduced capacity, his research at the Liggins Institute and his interest in science communication.

The new role started on July 1st. Professor Gluckman is a Distinguished Professor of Paediatric and Perinatal Biology and was Director of the Liggins Institute for Medical Research and the National Research Centre for Growth and Development at The University of Auckland until he took on this role.

His research assesses the factors during pregnancy that create a healthy start to life, especially how a baby's environment from conception to birth determines its childhood development and lifelong health.

Science Book Prize Announced

The winner of the inaugural Royal Society of New Zealand Science Book Prize was; The Awa Book of New Zealand Science.

Richard Dawkins, via video link from Britain, made the announcement in May during the Auckland Writers and Readers Festival.

The Awa Book of New Zealand Science is an anthology of writings about discoveries made by New Zealand scientists edited by Rebecca Priestley. All the writing is the scientists' own writing. Some of the scientists included were Ernest Rutherford, Brian Mason, Athol Rafter and Alan MacDiarmid.

The judges of the prize were Professor Jean Fleming (University of Otago), Associate Professor Harry Ricketts (Victoria University) and Professor Brian Boyd (University of Auckland). Rebecca Priestley received $10,000 for the prize and Awa Press $2,500.

The Awa Book of New Zealand Science is widely available for around $50.

Marsden Fund at its Highest

The Budget announced on 28 May added a further $9 million to the Marsden Fund.

This boost takes the total fund to its highest level of $47 million per annum.

This increase should mean over a dozen extra projects would receive funding each year.

Bid to Host International Astronomy Project

New Zealand and Australia are in the running to host the world's premier radio telescope project, the Square Kilometre Array Radio Telescope Project (SKA).

The host location will be decided in late 2011 or early 2012. Part of the project involves a series of around 5,000 telescopes to be constructed either across Australasia or Southern Africa.

Victoria University radio astronomer Melanie Johnston-Hollitt says an important part of the project is the research undertaken by radio astronomers generates spin-offs in software development, electronics, supercomputing, fibre optics, construction and manufacturing.

New Zealand will collaborate closely with Australia in the bid to host the telescope project.

Pet Food Brings Business and Research Groups Together

Protein Innovation NZ (PINZ) aims to make NZ a globally recognised leader in innovative meat science for pets.

AgResearch, Mars and Massey University launched the research consortium in May. Its aim is to better understand protein interactions and nutritional contributions of raw meat. The consortium also wants to work out how to use this knowledge to develop pet foods that are highly nutritious and can compete successfully in global markets.

Mars Petcare has a manufacturing site in Wanganui that supplies NZ, Australia and other Mars units in the Asia Pacific region.

It is also hoped further funding from AgResearch and Mars will ensure the PINZ group can develop a more fundamental understanding of raw meat materials.