Article

Environmental Aspects of the Disposal of Pharmaceuticals in New Zealand

Barrie M. Peake[a],* and Rhiannon Braund[b]

[a]Chemistry Department, University of Otago, PO Box 56, and [b]NZ National Pharmacy School, University of Otago, PO Box 913, Dunedin (e-mail: *bpeake@chemistry.otago.ac.nz*)

Introduction

The use of pharmaceuticals is on a global increase and NZ is no exception to this trend. The magnitude of this usage has led to an increasing international awareness of the disposal of pharmaceutical compounds, either to landfills or as sewage where they can have potential detrimental effects on the aquatic environment.[1] For example, trace levels of the contraceptive ethynylestradiol (**1**, Chart 1) found in waterways have been shown to impair sexual development and increase feminization of fish.[2] There is also evidence that the presence of antibiotics in waterways has impact on the bacteria present and may lead to antibiotic resistance.[3]

While researchers generally concur that the risk of acute toxicity of the pharmaceuticals at the levels found in water is negligible, the outcome of long term chronic exposure is less certain.[4] Many believe that as the detected levels are significantly below therapeutic levels there is no risk. However, this may not be true for all drugs and for all members of the public as the elderly, children, or those who have renal or hepatic impairment will be at increased risk.[2] As the production and use of pharmaceuticals continues to increase, the measurable levels in water systems will also increase. The question needs to be asked: *Is it acceptable to have active pharmaceuticals in drinking water even at subtherapeutic levels regardless of the predicted risks?*

It is not just the impact on human health that is relevant, but also that on other animals, marine life, and ecosystems. For example, environmental exposure of diclofenac (**2**) has been revealed as the cause of the declining vulture population in Pakistan.[5] Even our household pets may be at increased risk due to them having differing metabolic pathways. Thus, cats are deficient in the glucuronidation pathway and can accumulate and actually increase the half-life and toxicity of paracetamol (**3**) upon ingestion.[6]

The main sources of pharmaceutical contamination of water systems are humans (medications either ingested or improperly disposed of) and animals (veterinary treatments including medications),[7] but they can also include hospital wastewater and manufacturing facilities.[8]

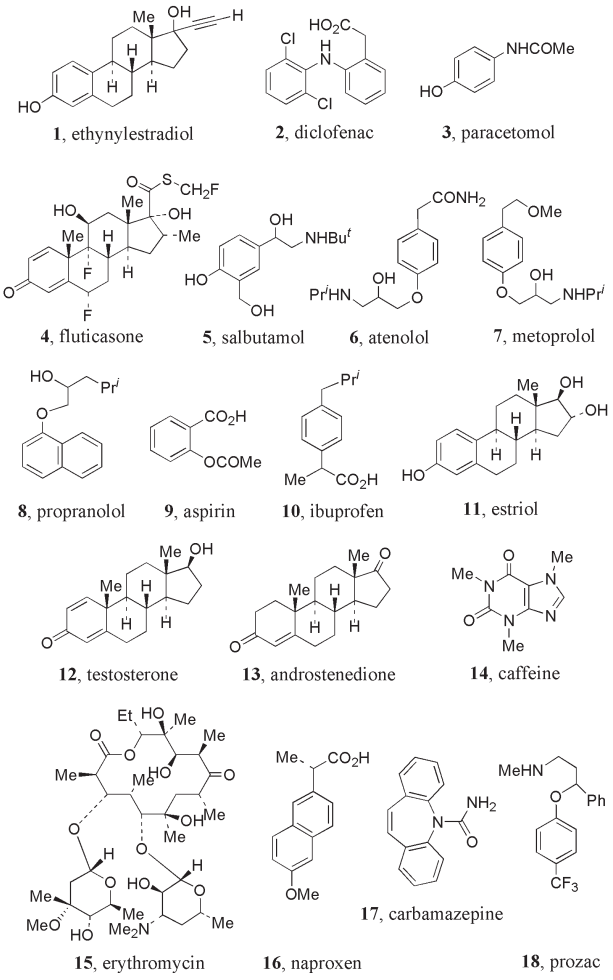
Disposal Pathways for Pharmaceuticals

The main pathways associated with the human disposal of pharmaceuticals that lead to their transport into the environment are summarised in Fig. 1.

Excretion

Pharmaceuticals can act either directly on various organs in the human body without any chemical modification or

Chart 1



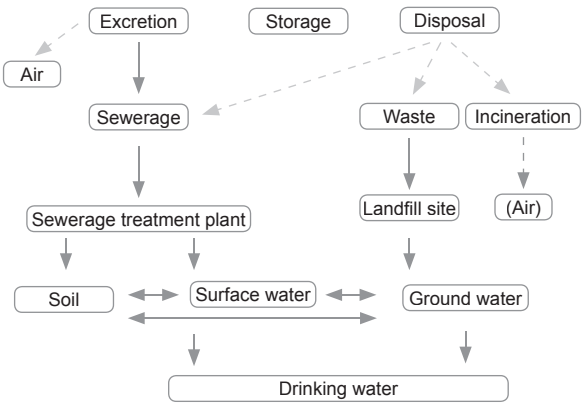


Fig.1. Potential pathways for entry of human pharmaceuticals into the environment (taken from European Medicines Agency Document EMEA/CHMP/SWP/444700, 2006).

they can be modified during their interaction. After their pharmacological action they are excreted in either an unchanged or modified form. Most pharmacologically active molecules are lipophilic and, following biotransformation, they are converted into water-soluble (and hence excretable) metabolites.[9] These metabolites are often less active than the parent compound although some may have enhanced activity or toxicity.[9] Additionally, many pharmaceuticals are excreted unmetabolised and in combination these products typically are discharged into sewage to be treated by a municipal authority.

A small fraction of human pharmaceuticals are used in a volatile liquid or gaseous form, *e.g.* inhalers used to treat asthma in NZ often contain fluticasone (**4**) or salbutamol (**5**) in an aerosol form. This can lead to the *excretion* into the atmosphere of the parent or metabolised forms, but rapid dilution with the air soon makes any subsequent environmental impact very unlikely.

Disposal of Unused Pharmaceuticals

Unused pharmaceuticals are either returned to the retail source or, more likely, disposed of as solid waste to a landfill or flushed down a toilet to become a component of liquid sewage. A study conducted in the US found that less than 2% of those surveyed returned unused medication to a pharmacy, 54% added them to household solid waste, and 35% disposed of them down the toilet or sink.[10] In the UK, 63% of those surveyed discarded unused medications in the household waste, 22% returned them to a pharmacy and 11% emptied them into the sink or toilet.[11]

Landfill and Sewage Treatment of Pharmaceutical Waste

Once a pharmaceutical compound is deposited as a solid in a landfill it is subject to all of the aerobic and anaerobic degradation processes that occur for any other type of organic solid waste. These lead to the formation of an organic-rich liquid leachate that can be contained or released in a controlled manner onto nearby soil, where it can make a contribution to the groundwater, or into a natural river course, where it is rapidly diluted. Studies conducted in the US have shown that landfill leachate can be a significant source of organic waste water contaminants and that the detected concentrations decreased along a gradient from a landfill.[12] To lessen this effect, many states are now recommending the disposal of pharmaceuticals in plastic containers before entry into the landfill to reduce the leaching of pharmaceuticals. While these plastic containers can remain undegraded for decades,[13] they can only delay the environmental exposure of the pharmaceuticals. If the organic material in a landfill is incinerated, then the pharmaceuticals present are combusted largely to form harmless gases that rapidly disperse in the atmosphere.

Conventional sewage treatment facilities involving primary and secondary treatment were never designed specifically to remove pharmaceuticals and, given their variable physical and chemical properties, their removal efficiency varies substantially.[1,8,14-17] The solid digested sludge can be spread on land or buried in a landfill, while the treated effluent is typically discharged into a natural waterway such as a river, lake, estuary or the open ocean. These aquatic systems can, in time, become the source of drinking water for humans, yet conventional drinking water treatment processes also have been found to be ineffective in removing many of these trace pharmaceuticals.[18,19] A specific example is the common *β*-blocker drugs atenolol (**6**), metoprolol (**7**) and propranolol (**8**) which have been widely detected in the aquatic environment.[14,20] Less than 10% of both **6** and **7** is removed by conventional sewage treatment using activated sludge.[21]

Environmental Impact (Ecotoxicology) arising from Pharmaceutical Usage

In assessing the likely impact of pharmaceuticals discharged into the environment, an important question is: *What is the ecotoxicological impact of the parent compounds or their metabolites and any degradation products arising from the treatment of the waste water containing these compounds?*[22] Some of the potential adverse effects that have been identified include lethal and sub-lethal toxicity on aquatic organisms, resistance development in pathogenic bacteria, genotoxicity, and endocrine disruption.[1,23-25] It is also important to consider the stability of these compounds in water,[26] and the potential for their bioaccumulation in marine life.[2]

One of the most common pharmaceuticals typically observed throughout the world in aquatic environments such as raw and treated sewage is the non-steroidal anti-inflammatory drug (NSAID) diclofenac (**2**, Chart 1). Median concentrations of **2** of 0.81 μg/L have been measured in municipal sewage treatment plant (STP) effluents and 0.15 μg/L in rivers and streams in Germany.[14] The sub-lethal toxic effects of this drug have been studied on rainbow trout (*Oncorhynchus mykiss*) by exposing them to concentrations of **2** in the range 1–500 μg/L over a 28 day period.[4] Histological changes were observed in kidneys and gills with the lowest observed effect occurring at a concentration of 5 μg/L. However, significant concentration-related bioaccumulation of **2** occurs in the liver, kidney gills and muscle of the trout. This suggests that prolonged exposure to environmentally relevant concentrations of **2** would lead to an impairment of the general health condition of the fish. Such an effect, however, is much less dramatic than the massive population decline reported for Indian vultures that fed on carrion of diclofenac-treated domestic livestock and cattle.[5]

Although the concentrations of individual pharmaceuticals can now be relatively easily measured, it is also important to remember that leachate and sewage waste streams contain a very large number of pharmaceutical components and such mixtures of pharmaceuticals may lead to additive or synergistic ecotoxicological effects. For example, NSAIDs including aspirin (**9**), diclofenac (**2**), and ibuprofen (**10**) have an estimated annual production of several kilotons worldwide. In ecotoxicity tests their toxicities in combination were considerable despite their individual toxicities being low.[27]

The current knowledge of the effects of trace amounts of pharmaceutical compounds in aquatic systems on the behaviours of a wide range of organisms has been summarised, but it is acknowledged that the information is

sparse and limited to a few substances and organisms.[22,28] The environmental concentrations of pharmaceuticals have been measured and generally fall within a range 10^3-10^7 times lower than the known LC_{50} or EC_{50} values for various organisms. Hence it is unlikely that lethal or acute toxicity effects will occur. However, the example of **2** in trout discussed above suggests that many presently unrecognised sub-lethal or chronic toxic effects may still occur.

A risk assessment database has recently been established to evaluate the potential risks of pharmaceutical contaminants in the environment with a focus on marine and estuarine environments.[29] The compounds are ranked using five different combinations of physicochemical and toxicological data that emphasise different risks. The results suggested that drugs used to treat infections pose the greatest risk to the environment. However, in setting up this database it became clear that there were still significant gaps in the knowledge available to accurately predict the impact of many other pharmaceuticals on the environment.

Chemical Aspects

Analytical Determination of Trace Levels of Pharmaceuticals

In order to assess the real or potential impact of the discharge of pharmaceuticals into the environment, it is essential to establish the concentrations of the parent and metabolised forms of these compounds in waste streams that discharge into the environment. This task is currently impossible for a landfill given the extreme heterogeneity of the solid contents. Atmospheric levels are so low as to be undetectable with current analytical instrumentation. Instead, much research[30-32] has been undertaken to develop methods for accurately and precisely measuring their typically very low levels in liquid streams associated with either landfill leachate or treated and untreated forms of sewage. Most of these methods, like that detailed below,[33] involve the extraction of the lipophilic pharmaceuticals using solid-phase extraction, separation by liquid chromatography, and detection using some form of mass spectrometry, *e.g.* LC-MS-MS. The limits of instrument detection in the separation and quantification of 27 such compounds in a diverse group of pharmaceuticals, steroids, pesticides, and personal care products were reported to be < 1.0 pg (<1.0 x 10^{-12} g) and recoveries of most compounds were >80%.

Observed Trace Levels of Pharmaceuticals in Waste Waters

The analysis of waste water to determine the trace levels of pharmaceuticals has developed only over the last 10-15 years following the pioneering study of German waste water (1998),[14] in Italy (2000),[34] and in a wide range of US streams (1999-2000) by the US Geological Survey.[35]

Other countries for which studies have been reported[36] of the concentrations of selected pharmaceuticals in various natural waters include Brazil,[15] the Netherlands, Switzerland, Spain, Finland, Canada[15,36] and Italy,[37] Mexico,[38] South Korea,[39] and Australia.[40,41] Typical levels reported for a range of different types of water in overseas countries for some of the common pharmaceuticals used in NZ (Table 1) are listed in Table 2.[26,35,38,40,42,43]

Strategies for the selection of those pharmaceuticals to monitor in natural waters have involved those based on calculation of sales volumes multiplied by percentage of metabolic excretion,[7,44] those that had previously been measured in water,[37] and those that were likely to be problematic due to high activity and potential activity even at low usage volumes.[7] A list of *priority pharmaceuticals* that have been selected for analysis in Italian waste waters has been described by Castiglionoi *et al*.[32]

Sewage Treatment Processes

As noted above, many conventional waste treatment processes such as those involved in primary or secondary waste water treatment, have minimal, if any, effect in degrading pharmaceuticals. Hence there is a significant current research effort to develop new processes that can degrade them to levels that are likely to have minimal environmental impact. Typically, more advanced (tertiary) treatment methods have been developed to degrade pharmaceuticals in the aquatic environment[45] that include membrane filtration, such as nanofiltration and reverse osmosis,[16,46,47] and activated carbon adsorption.[18,39] For example, a membrane filter system is in removing hormone compounds such as estriol (**11**), testosterone (**12**) and androstenedione (**13**), and certain pharmaceuticals such as paracetamol (**3**), ibuprofen (**10**) and caffeine (**14**) from sewage influent.[39] However, this membrane treatment did

Typical method for the extraction and analysis of pharmaceuticals from natural water sources; see ref. 33

1. Collect ≥ 1 L of natural water, *e.g.* sewage influent and effluent, groundwater, estuarine water, in a clean, darkened glass container.
2. Adjust the pH to < 2 using conc. H_2SO_4 to minimize degradation of the analyte(s) during storage at 4 °C.
3. Extract the analytes by loading 1 L of water sample on a pre-conditioned Waters HLB solid phase extraction cartridge, elute with methanol followed by a 1:9 mixture of methanol/*t*-butyl methyl ether (MTBE).
4. Add appropriate amounts of internal reference pharmaceutical compounds.
5. Concentrate the eluate to a volume of 1 mL using a stream of N_2.
6. Separate the analytes using a Synergi Max–RP C12 column and a binary gradient involving 0.1 % HCO_2H in H_2O and 100 % MeOH.
7. Analyze a 10 μL sample using an Applied Biosystems Model API 4000 triple quadrupole tandem mass spectrometer in one of the three modes: ESI positive, ESI negative or APCI positive.

Table 1. Top 15 NZ pharmaceuticals by number of prescriptions dispensed between July 2006 and June 2007.[a]

Rank	*Common Name*	*Treatment Condition*
1	Paracetamol	Analgesic/Antipyretic
2	Aspirin	Analgesic/Anti-platelet
3	Simvastatin	Cholesterol and cardiovascular control
4	Omeprazole	Dyspepsia, peptic ulcer disease
5	Amoxycillin	Broad spectrum antibiotic
6	Amoxycillin clauvulanate	Broad spectrum antibiotic
7	Metoprolol succinate	*β*- blocker (blood pressure control)
8	Salbutamol	Asthma (inhaled)
9	Diclofenac sodium	Analgesic/Anti-inflammatory
10	Cilazapril	ACE inhibitor
11	Frusemide	Diuretic
12	Bendrofluazide	Diuretic
13	Quinapril	ACE inhibitor
14	Fluticasone	Asthma (inhaled)
15	Prednisone	Steroid

[a]Data kindly provided by Pharmac NZ

Table 2. Concentrations in overseas natural waters of pharmaceuticals commonly prescribed in NZ (2006-07).

Pharmaceutical	*Country*	*Water Type*	*Typical Conc. (ng/L)*	*Ref.*
Paracetamol	Australia	STP[a] influent	8.1-23.3	40
"	USA	streams	110	35
Aspirin	Australia	STP influent	9.0-38.5	40
Simvastatin	USA	surface water	< 4 (LOD)[b]	42
Omeprazole	Spain	STP influent	2.17	43
Amoxycillin	Italy	STP influent	4.7	26
Metoprolol	Mexico	STP influent	210-250	38
Salbutamol	Italy	river	2.5	26
Diclofenac	Mexico	STP influent	250-340	38
Frusemide	Italy	river	255	26
Fluticasone	USA	surface water	< 13 (LOD)	42
Prednisone	USA	surface water	< 2.2 (LOD)	42

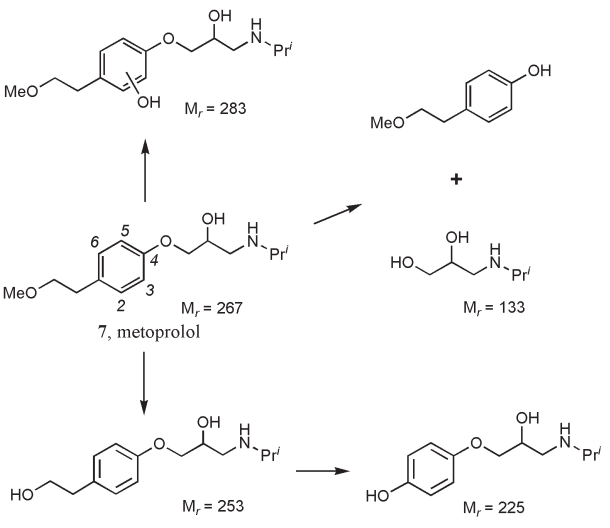
[a]STP: sewage treatment plant [b]LOD: limit of detection reported

not decrease the concentrations of other pharmaceuticals such as erythromycin (**15**), naproxen (**16**), diclofenac (**2**) and carbamazepine (**17**) as previously noted.[15,16] In comparison, reverse osmosis and nanofiltration processes show removal rates in excess of 99 % for all of these pharmaceutical compounds from sewage influent.

Nonetheless, there are issues that can complicate the successful implementation of these treatment processes, *e.g.* reverse osmosis and activated carbon adsorption require a high input of energy and material.[48] Similarly, it has been noted that many pharmaceutical compounds are polar and thus less likely to removed by the hydrophobic interactions involved in carbon absorption.[49] Recent studies conducted in Australia compared different wastewater recycling schemes to determine the impact of the treatment processes and found that the addition of reverse osmosis technology can concentrate many of the compounds of concern.[40.41]

Other successful tertiary treatments, including advanced oxidation processes (AOPs) involving the reaction of the very strong hydroxyl radical (•OH) oxidant and/or the solvated electron (e_{aq}^-) are also effective in removing many pharmaceutical compounds from waste water.[18,50] These reactive species can be generated by chemical reactions involving a range of chemical agents such as O_3, H_2O_2, transition metals, *e.g.* Fe^{2+} – Fenton reaction, and metal oxides, *e.g.* TiO_2, together with auxiliary energy sources such as UV-visible radiation, electron beam, γ-radiation and ultrasound. Thus, the *β*-blocker metoprolol (**7**) present in waste water is only degraded by 10% using conventional activated sludge treatment,[21] but it can be removed efficiently from aqueous solution by reaction with •OH and e_{aq}^- produced by an electron beam.[51] The degradation products were separated and detected with LC-MS techniques leading to the degradation pathway of Scheme 1. Of course nothing is known about the ecotoxicty of the degradation products and so the overall assessment of how eco-friendly this advanced oxidation process might be in reducing the levels of metoprolol in natural water remains unknown.

Photochemical AOP reaction can be affected by anything present in the water that absorbs or reflects the incident light. Variable levels of dissolved organic matter, carbonate, bicarbonate, and chloride ions are always present in all naturally occurring waters and these species can also react with •OH and e_{aq}^- to reduce significantly the overall efficiency of the removal of trace levels of pharmaceuticals.[52]



Scheme 1. Degradation products and proposed reaction pathways for •OH oxidation of metoprolol - see ref. 64

Modelling Pharmaceutical Concentrations in Raw and Treated Sewage

An alternative to actually measuring the trace levels of pharmaceutical compounds in raw sewage after various levels of treatment is to calculate these levels. Such an approach has been reported[53] using fugacity modelling and data on i) pharmaceuticals usage (prescription records), ii) human metabolism and excretion of pharmaceutical residues, iii) the chemical and physical properties of the compounds, and iv) information on the design and operating characteristics of the sewage treatment process. This model was successfully tested using Australian data from which 29 of the *top-50* most commonly dispensed pharmaceuticals were predicted to be present in raw sewage influent at concentrations of ≥ 1 μg/L while 20 of the compounds were predicted to remain at effluent concentrations of ≥ 1 μg/L after secondary treatment. While it was conceded that the model *possesses a high degree of uncertainty*, it was a useful screening tool for providing a) a basis for estimating any correspondence between the quantities of prescribed pharmaceuticals and their observed concentrations, b) an estimate of concentration and likely distribution of compounds that have not been measured, and c) an indication of likely future effluent concentrations of any new drugs.

Green Chemistry

In the current era of environmental sustainability, the rapidly developing area of chemistry described as *the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances* (green chemistry) clearly is very relevant to any chemical process that can degrade and detoxify pharmaceutical compounds discharged into the environment.[28] Current *green processes* that might be used for the treatment of waste- or drinking-water include all of the ozone-based advanced oxidation processes, *viz*.(O_3 and O_3/H_2O_2 with and without UV light). The Fe-TAML activation of peroxide[54] has also been found to degrade recalcitrant pharmaceuticals such as fluoxetine (**18**)[55] and a range of estradiol-based hormone compounds.[56]

Of course, the ultimate Green Chemistry challenge as identified by Khetan and Collins[30] would be to design pharmaceuticals that contain a structural component that is unreactive in the human body while treating an ailment, but *turned on* to become reactive when the compound or its metabolites are excreted and released into the environment. Alternatively, this special structural component might enhance removal of the compound once it is present in the waste water undergoing treatment in a sewage plant using a selective process such as surface adsorption.

Conclusions

The profession needs to be proactive now rather than reactive when a health problem emerges. We need to determine the key contributors and/or potentially harmful compounds, and put processes in place that minimise their entry into the waterways.

There appears to be almost nothing known about the levels of pharmaceuticals disposed in the NZ environment or of the impact they have. Although annual data on the quantities of various pharmaceuticals sold in NZ are available from Pharmac (see Table 1), there appears to be no published measurements on the levels of these compounds in NZ waste streams either in parent form or in degraded form(s). Moreover, the recent Ministry for the Environment publication *Environment New Zealand 2007* that updates the state of NZ's environment,[57] has no mention of the levels of possible organic contaminants arising from the use of pharmaceuticals. Seemingly there are no limits currently specified in the resource consent monitoring conditions for maximum allowed levels of *specific* pharmaceutical compounds in the effluent discharged from sewage treatment plants in this country. However, current overseas research clearly indicates that even trace levels of some of the compounds likely to be present in NZ waste water (based on Pharmac records) can have a potential detrimental effect on the environment by affecting aspects of biological activity. They could also affect the quality of NZ drinking water obtained from groundwater and other natural sources. If NZ is to maintain its international *clean green image*, then it is essential that all aspects of pharmaceutical use and disposal in NZ are investigated.

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Darwin Celebrated

Charles Darwin's legacy was celebrated in Auckland on the 200th anniversary of his birth.

Darwin was born on February 12 1809 and on February 12 2009, a free public symposium; "(R)evolution – a Celebration of Darwin", was held at Auckland University.

The day included speakers discussing the impacts of Darwin on various areas of science as well as the humanities. Professor Brian Boyd (pictured) from the Auckland University English Department gave a talk on imagination and story telling in the evolution of humans.

A poster competition was held for graduate students involved in evolution research. This was won by Katie Hartnup from Massey University with her poster; "Historical DNA analysis of kiwi feather cloaks: Kahu Kiwi".

The event was well attended with the 600-seat Fisher & Paykel Appliance Auditorium full and overflowing into another venue for some of the talks. Three hundred secondary school students were part of those present. Organiser, Professor Allen Rodrigo (pictured) from the University's Biological Sciences Department, was delighted at the response.

Other events to celebrate Darwin included a series of lectures in March by Dr Frans B. M. de Waal that started with; "Our Inner ape – Morality: A Darwinian view of the moral emotions in man and animals" and also covered empathy and culture. In May a two day course entitled "Resolving the Creation versus Evolution Controversy" is also being held.

Allen Rodrigo and Brian Boyd at the symposium (Picture credit: University of Auckland photographer, Godfrey Boehnke)