# Biomedicals from Bone

Michael R. Mucalo[a] and Andrew J. Worth[b]

[a]Chemistry Department, Waikato University, Private Bag 3105, Hamilton 3240 and [b]Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North (email: *m.mucalo@waikato.ac.nz*)

## Introduction

The realm of biomaterials, under which biomedical materials can be categorised, has a broad definition base and recognises materials that are synthesized or naturally sourced. Biomaterials are normally those that come into contact with live tissue and physiological fluids. They have applications as prostheses to replace lost function of joints or to replace bone tissue, for diagnosing medical conditions, as a form of therapy, or as a storage unit.[1] The diversity and scope of biomaterials science research, and especially its application to the improvement of trauma, disease, and congenital defects in the human condition, are making this branch of science increasingly dominant and topical in many countries. An exciting aspect is that such research is interdisciplinary. The varied problems of the human condition that biomaterials research addresses occupy the efforts not only of medical doctors who act as the end users of such technology, but also those of chemists, physicists, engineers, and biologists in creating the technological advances. Chemistry, in particular, plays a major role in such research, after all it is the foundation stone on which biomaterials polymer science and biomedical scaffold materials are built.

The replacement of any bone due to disease or trauma needs an implant. This implant can fall under one of three categories: autograft (fresh, living bone tissue harvested from somewhere else on the patient's body such as the hip), allograft (living bone tissue donated by other individuals that is sourced from a *bone bank*, or xenograft (a synthetic bone substitute that lacks any living component but which could potentially act as a *scaffold* to support cells, *etc*. While autografts represent the *gold standard* of bone implants in terms of minimisation of rejection issues, the pain of bone harvesting and the limitations of how much to harvest are disadvantageous. Allografts, alternative bone replacement materials, can have body rejection issues that couple with risks of disease transmission and paucity of material available for implants. The rationale, therefore, for development of xenograft materials is to reduce reliance on autograft and allograft bone. Within the area of biomedical materials, the quest for suitable materials that act as *osteoconductive* xenograft scaffolds *viz*. ones capable of supporting new bone deposition and its proliferation, has been an avid subject globally. The keenness of interest in xenograft implantation materials in general has been further accentuated by the recently emerging area of *Tissue Engineering* which, according to Langer and Vacanti[2] (the pioneering scientists in the field) *applies the principles of biology and engineering to the development of functional substitutes for damaged tissue*. In contrast to conventional xenograft scaffold research, the *scaffold* referred to in Tissue Engineering is effectively a biodegradable (usually polymeric) three dimensional device. It serves as a cell transplant vehicle for bringing about formation of the structural and functional tissue units by the cells that have been transplanted.

## Bone and its Chemical and Morphological Characteristics

Bone is a living interdigitated (or interlayered) composite of collagen protein and calcium phosphate platelets, the main mineral phase of which is carbonated *calcium hydroxyapatite*. Calcium hydroxyapatite, stoichiometrically $Ca_{10}(PO_4)_6(OH)_2$, is the *hydroxy end group member* of the complex apatite family and it has a more complex chemistry than the related fluorapatite and chlorapatite compounds. When prepared by precipitation from aqueous solution, the Ca:P ratio varies from 1.50-1.66 rather than being reproducibly 1.67, the value expected from its stoichiometry.[3] Structures categorised as being part of the apatite family have had their generic descriptor coined from the Greek word apato - deceit.[4] They have the characteristic and interesting property of substitutional lability in that the cationic and anionic components of the lattice structure, *e.g.* the $-PO_4$, -OH and $Ca_{2+}$, can be partially replaced with others when in solutions containing exchangeable ions. When lattice substitutions occur in calcium hydroxyapatite, the physical properties of the solids, *i.e.* their solubility and crystal morphology, can change markedly from the state prior to the lattice substitutions. Biomineralization processes lead to bone deposition in the body and they occur in a complex physiological fluid. The composition of the mineralized apatitic portion of bone is not stoichiometrically pure but rather it exists as a carbonated calcium hydroxyapatite doped with various other inorganic elements and/or organic ions. It was proposed in 1958 by Neuman *et al*.[5] that the mean composition of *bone* was $[Ca_9(H_3O)_2(PO_4)_6][Ca, Mg_{0.3},Na_{0.3},CO_3, citrate_{0.3}]$. A more recent report[6] has stated that its chemical composition can be approximately given by $Ca_{8.3}\square_{0.7}(PO_4)_{4.3}(HPO_4$ and $CO_3)_{1.7}$ (2OH and $CO_3)_{0.15}\square_{1.7}$ where $\square$ can equate to a lattice vacancy. In reality, it is difficult to give an exact composition of bone as it varies with species, the age of the vertebrate, and the location of bone in the body. Bone also has a specific architecture consisting of *cortical* bone, the harder outer layer of bone, and *cancellous* bone, which is described as being the softer, spongier porous portion residing inside the bone. The cancellous architecture is created by deposition and resorption processes that occur during bone formation as a result of the actions of bone tissue-associated cells such as osteoblasts, osteoclasts and osteoblasts.[7] The overall porous architecture of bone that acts as a hard tissue support for the cellular or *parenchymal* (living) component of bone is characterised by its interconnected porous channels, known as the *trabecular network*, that allow the transport of blood

through this living tissue.[8]

Any hard tissue replacement material for bone must thus attempt to replicate the typical bone architecture and be composed preferably of calcium phosphate materials that are not only biocompatible with the body but also able to be *remodelled* interfacially. This then allows a) new bone-apatite to be co-deposited with collagen after a process of dissolution-re-precipitation of the bone-implant interface and, b) new bone tissue to penetrate the implant at the bone-implant interface to provide a securely bonded bone-implant interface that effectively lodges the bone in its position. The so-termed *bioactivity* of the bone replacement material is important as such materials allow a direct chemical bond (without any so-called intervening fibrous tissue) to occur between natural bone tissue and the implant. Calcium hydroxyapatites have this property. This contrasts directly with the so-called *bioinert* (or biotolerant) materials represented by *e.g.* hard ceramics such as alumina, zirconia, stainless steel, and titanium. These *bond* to bone tissue purely through an intervening fibrous tissue layer of varying thickness which separates natural bone tissue from the implant.[8] Given these needed attributes for bone tissue replacement, cancellous bovine bone arguably is the ideal, almost ready-to-use material. After processing (see below), this bone already possesses the desired mineral composition and the necessary architecture to allow bone modelling at its interface as well as tissue in-growth.

Our main focus on producing xenograft bone replacement materials has been to use the plentiful and relatively low cost animal bone from our large cattle herds. This can be done in NZ because of the strict auditing/tracking and MAF/biosecurity procedures that show the country, historically, not to have had any serious, notifiable diseases afflicting its herds and especially *Bovine Spongiform Encephalopathy* (BSE). It has been allegedly that consumption of meat affected with this disease led to human contraction of the fatal brain-wasting disease known as *variant-Creuztfeldt-Jacob disease* (*v*-CJD) in the UK. The continued BSE-free status of NZ (and Australia) allows bone material for biomedical applications to be sourced from the country's mainstream cattle herds rather than from expensive controlled herds, *viz*. specially selected and certifiably BSE-free, that have to be used overseas for bone-sourced biomedical materials such as Bio-Oss®.[9,10] From the NZ perspective, this has the potential to produce a cheaper, high value biomedical commodity out of a traditionally low value material currently used for fertiliser or disposed of into the environment.

## Processing Bovine Bone into Xenograft Cubes or Powders

The work performed at MIRINZ (NZ Meat Industry Research Institute) and Waikato's Chemistry Department in generating xenograft materials and powders from bovine bone has been described previously and the serious reader is directed to the literature.[10,11]

### *Xenografts*

For the preparation of xenografts, it is necessary to cut cubes of cancellous bone from the *condyle* portion of the bovine femur bone using a sharp band saw. The condyle is the rounded part of a bone (here, the femoral bone of a bovine that supports its bulk) that fits into the socket of another bone to form a joint. The reason bovine condyles are suited to forming xenograft cubes lies in the relatively large size of the condyles. There is enough cancellous bone in a typical (mature) bovine condyle to produce three to four cubes of materials *ca*. 25 $mm^3$ each, by cutting.[10] Other species of animals common to NZ agriculture such as sheep, deer, or even ostriches have femoral condyles which are either too small (sheep and deer) to allow the cutting or are overly spongy with a high fat content (ostrich). Bone from other parts of the bovine skeleton, such as the rib can be processed, but it is more useful for forming re-precipitated hydroxyapatite powders by acid dissolution processes rather than as xenografts.

In cutting the cubes, only frozen femoral condyles from supermarket abattoirs are used so as to have minimal sealing of the bone pores by frictional heat-induced collagen-to-gelatin transformation during cutting. The bone cubes are then boiled in water (conventional pressure cooker for 6 h and *ca*. 15 psi) to remove the bulk of the blood and fat present in the cubes. Initial work[10,11] at Waikato involved pressure cooking of the bones followed by a 16 h soak in NaOH, water rinse, and microwave heating of the bones (in water) to bp (to assist in fat removal). The bone cubes were then refluxed in AcOMe, which has a high affinity for fat, and then vigorous shaken or blown with compressed air to remove excess liquid prior to final drying. Cubes that contain fat are yellowed in appearance (Fig. 1). Deproteination of the defatted cubes was the next processing step and this was achieved by immersing the defatted cubes in simple oxidising agents (NaOCl or $H_2O_2$). This removes the bulk of the collagen protein which, when interdigitated with carbonated hydroxyapatite, gives the bovine bone a considerable degree of hardness. Bone containing fat is yellow, defatted bone less so, but that with the protein removed has a whitened chalky consistency (Fig. 1). The last corresponds to carbonated hydroxyapatite with a significant loss in mechanical strength.[12] This attribute means that it can be shaped for the desired implant by using a knife, scissors or a trephine (Fig. 1 shows a shaped implant).

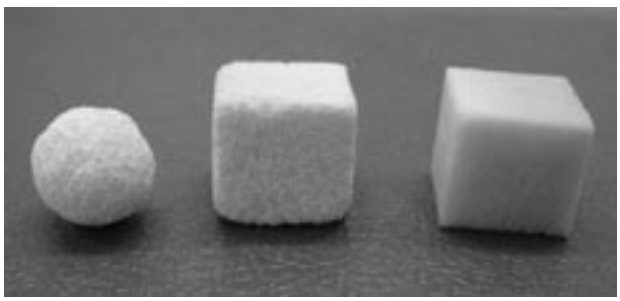

***Fig. 1.*** Bovine cancellous bone specimens. R to L: bovine cancellous bone cube prior to reflux with MeOAc showing the yellow colouration due to fat, defatted and deproteinated bovine cancellous bone as a bleached and chalky cube, and a shaped piece of defatted and deproteinated bone.

In later research carried out by Mucalo and Foster[13] and continued currently by Laird, Mucalo and Dias,[14] the pressure cooked bone was not subjected to the time consuming solvent-assisted defatting and bleach-assisted deproteination procedures. Instead it was placed in alumina crucibles and sintered at 1000 ºC in a muffler furnace for several hours to burn off organic matter and leave the brittle white mineral shell of the bone intact with its porous architecture (Fig. 2). Under these conditions, the bone mineral transforms from partially crystalline carbonated hydroxyapatite into crystalline hydroxyapatite.

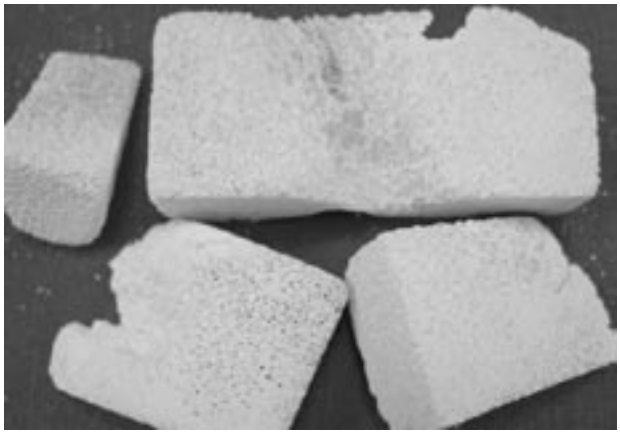

***Fig.2.*** Bovine cancellous bone after sintering at 1000ºC for 3 h.

### *Powders*

A variety of methods have been used at Waikato to produce powders from bone.[11] In previous studies milled animal bone powder was produced directly by crushing raw bone from a variety of available animal types, *e.g.* rib bones, sheep, bovine, corvine bone, *etc*., in a hydraulic press at 100 psi and then pressure cooking for 4 h to remove tissue and fat. After drying the bone chips were ground further in a hammer mill to particle sizes <2 mm diam. Further processing, such as AcOMe reflux (to remove further traces of fat), NaOH treatment, or more commonly acid-dissolution/re-precipitation (using NaOH) was then possible.

Although the acid-dissolution/re-precipitation methods produced powders, the residual fat and protein by-products arising from using raw bone as a starting material produced many problems, even when an intervening pressure cooking step was used. For example, performing the acid digestions in $HNO_3$ led to orange colouration of the resultant hydroxyapatite powders due to so-called xanthoproteic reactions,[13] which arise from interactions of the protein residues in collagen with the $HNO_3$. Even HCl digestions (in which xanthoproteic reactions are absent) of the milled bone powders led to opaqueness, most likely due to suspended collagen or fat. To remedy this, research by Mucalo and Foster[13] involving cleaner acid digestion/re-precipitation of already sintered bone pieces was performed. This minimized problematic bone matrix-associated organic impurities by the burn off of these. Cleaner, white powders were obtained, especially from the $HNO_3$ dilutions, leaving only the washing out of $NO_3^-$ from the powders after re-precipitation in the subsequent cleanup process. Subsequently, the process developed[14] was employed to provide kg-scale re-precipitated hydroxyapatite powders for plasma spraying. Here, the powders were passed through an Ar plasma under conditions where the re-precipitated hydroxyapatite particles become partially molten and can be impacted onto stainless steel or titanium metal surfaces to form a *plasma spray coating* (another biomedical type application).[15] Such coatings render metallic surfaces such as titanium or stainless steel more bioactive and give them the ability to bond more strongly to natural bone tissue through the mechanochemically bonded hydroxyapatite layer; an example of such a coating is shown in Fig. 3. The heterogeneous and porous nature of the plasma-sprayed hydroxyapatite coating not only improves the bioactivity of traditionally bioinert stainless steel or titanium substrates but may also provide a means of tissue in-growth so improving the bone-coating bonded interface.

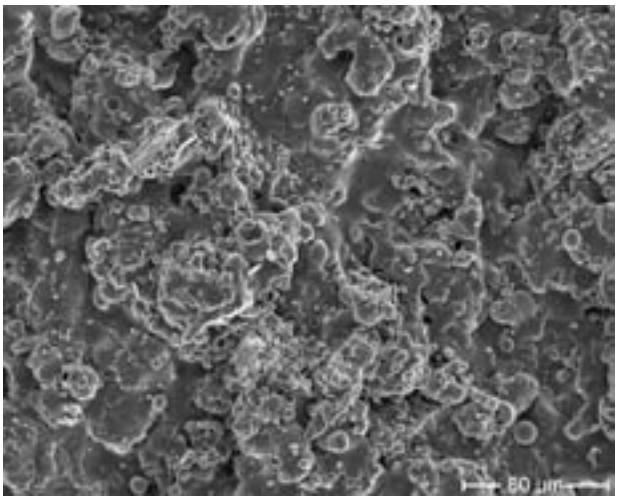

***Fig. 3.*** An SEM micrograph of plasma sprayed calcium hydroxyapatite coating on a titanium plate. The feedstock powder for this coating was produced by David Foster by re-precipitation from an acid digest of sintered NZ bovine bone.

## Spectroscopic and Microscopic Characterisation of the Xenografts and Powders Derived from Animal Bone

A wide range of spectroscopic, microscopic and other physical or mechanical testing techniques can be used to follow the chemical and physical changes that occur in the bone materials as they are processed for biomedical purposes. Thus, X-ray diffraction, solid state NMR and IR spectroscopy, atomic absorption spectroscopy (AAS), inductively coupled plasma optical emission spectrometry (ICP-OES), X-ray photoelectron spectrometry (XPS), scanning electron microscopy/energy dispersive X-ray analysis (SEM/EDXA), differential scanning calorimetry (DSC) and mechanical testing techniques (aimed at measuring the bulk modulus and yield stress values of the bone) have been used in our studies to characterise the bone matrices as a function of processing.[10-12]

Generally, IR, solid state magic angle spinning (MAS) $^{13}C$ NMR, and (to a lesser extent) XPS showed that the main changes during boiling/defatting/deproteination that led to the xenograft bone were due to the removal of fat and protein. As mentioned above, the remaining mineral residue retaining the original porous architecture of the

bone was hydroxycarbonate apatite.[10] This was confirmed by an IR spectrum of the crushed bone (Fig. 4) with peaks characteristic of carbonate at 1451 and 872 $cm^{-1}$ in addition to the apatitic phosphate-associated vibrational modes at 1036, 605 and 564 $cm^{-1}$, respectively. However, when the defatting and bleach-assisted deproteination are replaced by sintering the boiled bone at 1000ºC, the bone mineral remaining is no longer the partially crystalline carbonated hydroxyapatite apatite; transformation to crystalline calcium hydroxyapatite occurs (Fig. 5), as evidenced by weak peaks at *ca*. 1450 $cm^{-1}$ that indicate the carbonate stems from surface interactions between atmospheric $CO_2$ and CaO present within the sintered bone. SEM micrographs of boiled/defatted/bleach-deproteinated bone specimens showed the successful retention of the macroscopic structural detail of porous, cancellous bone along with the needed interconnected porosity channels for successful integration of the implant *in vivo*. For acid-digested/re-precipitated powders derived from bone, IR spectra show features typical of poorly crystalline calcium hydroxyapatite; remaining features are usually due to carbonates substituted into the calcium hydroxyapatite lattice structure. These latter carbonates can arise by $CO_2$ contamination during the alkali-induced re-precipitation.

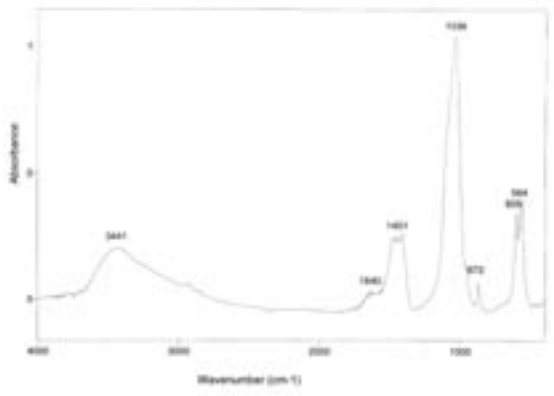

***Fig. 4.*** FTIR spectrum (KBr disk) of ground bovine cancellous bone after subjection to boiling/defatting and deproteination.

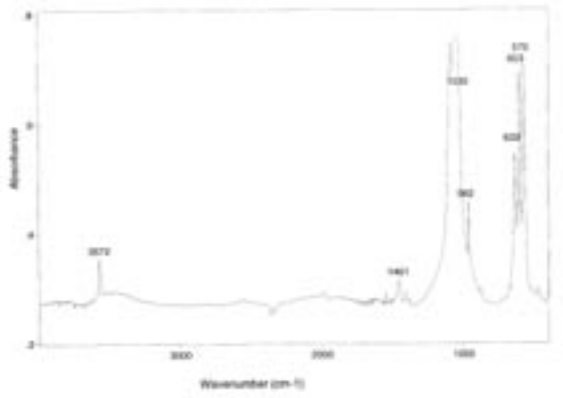

***Fig. 5.*** FTIR spectrum (KBr disk) of ground bovine cancellous bone after sintering at 1000ºC for 3 h.of the calcium hydroxyapatite from the acid digests.

Material strength tests predictably showed that prolonged boiling (6 h) followed by the deproteination hypochlorite treatment to give the chalky bone had a deleterious effect on the overall mechanical strength of the bovine bones tested.[12] This is desired because the xenograft material that results is easily shaped. It is important, however, not to over-process otherwise attempts at shaping can result in complete collapse of the xenograft due to extreme brittleness.

## *In vivo* Study of the Implanted Boiled/ Defatted/Deproteinated Bovine Bone in a Sheep Model

The success and safety of an implant acting as a bone substitute can only be demonstrated properly through a series of *in vitro* and subsequently *in vivo* testing procedures. *In vitro* testing involves subjecting the xenograft to a series of tests that evaluate its biocompatibility/irritation prior to placement in a living organism. One such widely used test is the hen's egg test-chorioallantoic membrane (HET-CAM) test. This is described as a biocompatibility test intermediate to classical *in vitro* and *in vivo* test protocols.[16] The test assesses the irritation potential of a particular substance by applying it directly to the highly vascularized chorioallantoic membrane of a developing chicken embryo that is <10 days old. Under these conditions there is no visibly noticeable embryo, rather a beating heart in the middle of a network of vasculature (Fig. 6) which would develop over time into a full sized chick embryo given the correct incubation conditions. A scoring system[16] evaluates the potential for tissue irritation, *e.g.* haemorrhaging by contact of the material with the blood vessels. Other tests that evaluate the material's biocompatibility for physiological environments involve the responses of cells (from specially grown cell lines) to contact with the implant materials.[17]

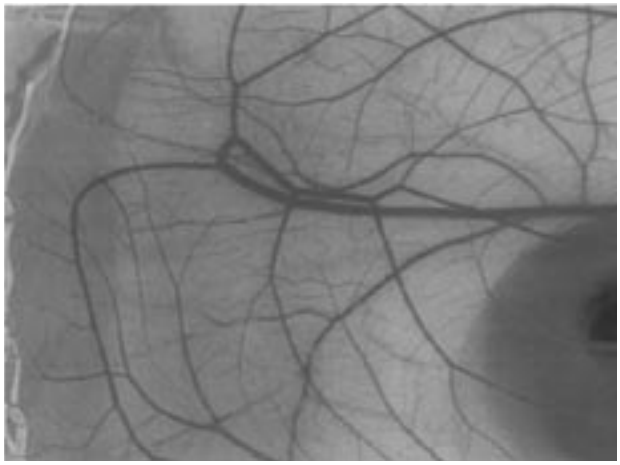

***Fig. 6.*** Hen egg chorioallantoic membrane (<10 days old) used to test materials for biocompatibility with living tissues. The dark image at right is the embryo chick heart. Typical test protocols note the response of the vasculature to the materials. Photo courtesy of Dr Kavitha Babu, AgResearch, Ruakura.

The boiling/defatting/deproteination process of bovine bone was presumed sufficient to render it immunologically inert for *in vitro* testing. One must note that fat removal is important because its presence in an implant can make it *antigenic*, *viz*.cause infection once surgically inserted.[18] However, the existing wide body of clinical knowledge

relating to *in vivo* bovine-derived materials in living organisms argued for a surgical protocol for *in vivo* implantation of the bovine bone xenografts. This was developed by Warrick Bruce and Geoffery Horne (Massey University and Wellington School of Medicine, respectively) and approved by the Massey Animal Ethics Council. Surgeries were carried out at Massey's Veterinary Teaching Hospital and the Wellington School of Medicine, and the Waikato bone cubes were implanted in an ovine femoral defect model to evaluate their efficacy as an osteoconductive bone graft; the details of this work have been described in the biomedical literature.[19] The surgical protocol involved the excising of an autograft bone sample from the sheep's femur so at to create a defect for the processed bovine *xenoimplant*. The excised autograft bone tissue was placed as a control in a defect created in the opposite femur of the same test animal. Twelve mature ewes with weights 55-70 kg were used in the study so as to avoid the normal growth processes of younger animals and minimize impact upon xenoimplant incorporation. The trephine implement removed 8 mm O.D. cylindrical cores of the xenoimplant from the (boiled/defatted/deproteinated) Waikato bone and this was sterilised (γ-radiation) prior to implantation. The deposition of new bone tissue around the implants was monitored at 15-17, 30-32, and 56 days after surgery using fluorochrome label dyes that had been intravenously introduced at certain time periods after the surgical implantation. The sheep were humanely euthanized ten weeks after surgery and the distal femurs harvested. De-muscled bone sections X-rayed and then non-decalcified thin sections embedded in resin for fluorescence microscopy study. Overall, the study supported bovine bone as osteoconductive in the ovine model used and the fluorescent labelling showed that new bone material grew over the implant. Furthermore, the xenoimplant performed similarly or *better* to the autograft in osteoconductivity. This unexpected observation has been ascribed tentatively to the open, porous nature of the bovine xenoimplant after trephining. This contrasts to the polished and sealed surface of the autograft which would have delayed tissue in-growth. In particular, the study has confirmed that boiled/defatted/deproteinated bovine bone is workable, easily shaped, and compatible to surgical procedure.

Further surgical work at Massey[20] implanted boiled/defatted/deproteinated bovine bone in a defective paw of a family's pet dog. The void in the dog's paw bone was cleaned out and replaced with a grafting mixture of autogenous cancellous bone and the Waikato xenoimplant. This procedure has as its ultimate aim not simply reducing dependence on the quantity of harvested autogenous bone needed but to use the osteoinductive properties of the autogenous bone for stimulation and propagation of bone growth and lead to bone growth in the osteoconductive xenoimplant portion of the graft.

The dog's paw was X-rayed post-operatively at 1, 2, 6, and 10 months and showed over this time overall densification of bone in the region of the void. The dog itself was sound throughout this period and is still believed to be alive today at time of writing. Thus the bone developed at Waikato has immediate use as a xenograft material for veterinary purposes.

## Current and Future Activities

Work at Massey University on implantations of the Waikato bovine bone in dogs continues while collaboration with Otago is on the development of a sintered bovine bone material with the strength lost by collagen removal partially restored. Biocompatibility testing of these materials using the HET-CAM, as well as separate trials employing a specific cell line, viz. L929 (to assess whether cells proliferate on these materials) would have been conducted by the time this article has gone to press. Eventually, an *in-vivo* implantation trial in a suitable animal model (likely sheep) will also be considered on the basis of the initial biocompatibility testing results.

## Conclusions

It has been shown that NZ-sourced bovine bone provides a useful bone replacement material for veterinary applications and holds strong promise in the future for human applications. Thus value has been added to what was formerly a low value resource in agriculture. Hopefully it will create a new, specialist niche export market for this country.

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# Do We Expect Too Much? Reflection on Chemistry Content in Higher Education†

Richard K. Coll

University of Waikato (e-mail: *r.coll@waikato.ac.nz*)

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## Learning Science

Education research in the 1970s, like other related areas, was dominated by quantitative work[1] during an era for which *social sciences* sought to draw upon the successful *scientific* approach typically used in the physical sciences (in particular) to investigate teaching and learning.[1,2] So if we felt a cohort of students did not understand some concept, we tried to find out whether or not a different teaching approach could *fix* their misconceptions.[3] But how to do this? Well, drawing on a scientific approach, we would divide the class or classes up, teach one cohort the same way we always had, and the other cohort in our new way, and evaluate any differences in conceptual understanding using, *e.g.* a standardized topic test. Differences would be examined for statistical significance of evidence that our new approach to teaching had worked. And this is the way much research was done at the time. Control of variables, randomized sampling, and so on, were all embedded in such an approach to educational research.

At about this time, however, key research – some of it NZ-based – suggested teaching and learning was rather more complex. Investigation into how students arrive at their own views of scientific concepts, focused on student misconceptions, or alternative conceptions, viz. students' views that are at variance with the accepted scientific viewpoint. Perhaps it is not that surprising that students harbour misconceptions for abstract concepts such as the kinetic theory, electricity, and force. But some student views of more common concepts are less easily understood and it is likely that they are influenced by other factors such as cultural background. There are some unusual examples reported in the literature. For example, one study of misconceptions of Papua-New Guinean students found some to believe that pregnancy occurs when a spirit child enters a woman rather than as a result of sexual intercourse.[4] A Caribbean-based study found that some students believed that hair would grow more rapidly if it was cut during the full moon.[5] Other researchers have suggested that some student misconceptions may arise as a result of the learning process itself.[6] These studies might seem curious or odd but, overall, such studies suggested that factors other than the school environment and the teaching processes used were also influential in student learning. There are now huge bibliographies of student alternative conceptions complied, some with several thousand studies detailed.[7]

What is perhaps of more concern is the *remarkable tenacity of many student misconceptions*. Students in many cases seem unwilling to give up their prior beliefs even after instruction.[8-10] Similarly, early research by Osborne and colleagues[10] suggested that even very able students, *i.e.* those who passed exams with high marks, did not actually understand fundamental scientific concepts in ways we would desire.

What might be the overall origins of such problems, and what might we do about it? Let me consider this by looking at what I think is a key factor; high, *perhaps unrealistic*, expectations of our students.

## Learning Chemistry in Higher Education

As mentioned above, considerable concern has been expressed in the literature about the high incidence, and remarkable tenacity, of common student misconceptions. The vast bulk of this research is concerned with school students, but similar issues are reported also for students of advanced chemistry from the higher education sector. Some higher education research reports give a real sense of frustration experienced by teachers or lecturers as they struggle to deal with student misconceptions.[11-16] While there are a number of concepts that students traditionally find difficult such as aspects of physical chemistry, like thermodynamics and electrochemistry,[11] researchers seem more concerned at the prevalence of student misconceptions for *even very simple concepts*[12,15,16] For example Herron[16] comments that for his first-year chemistry students *fewer than 50% of the students seemed to comprehend that it was $Cl^-$ that was in table salt and not $Cl_2$ or that*