Endocrine and paracrine regulation of bone

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Dr Thomas John Martin is Emeritus Professor of Medicine at the University of Melbourne (Melbourne, Australia) and John Holt Fellow at St Vincent's Institute of Medical Research (Victoria, Australia). After being Professor of Chemical Pathology at the University of Sheffield (Sheffield, UK) from 1974 until 1977, he was Professor and Chairman of the University of Melbourne Department of Medicine until 1999. He was Director of St Vincent's Institute of Medical Research from 1988 to 2002. His research has focused on bone cell biology, the mechanisms of action of hormones that influence bone and calcium metabolism, intercellular communication in bone and the differentiation of bone cells, and the effects of cancers upon the skeleton. A Fellow of the Royal Society and of the Australian Academy of Science, he has been President of the International Bone and Mineral Society and is currently Vice President of the International Cancer and Bone Society. Among the awards he has received are the Dale Medal in 1992 (UK), the Chemofux Research Prize in 1988 (Vienna, Austria), the William F Neuman Award in 1994 (USA), the Ramaciotti Award in 2004, and the Gideon A Rodan Award for mentorship in 2007. He has published more than 600 scientific articles and reviews and six books.

What led to you focusing your research on bone–endocrine biology?

Four years after graduating, I went to work in Chemical Pathology at the Royal Postgraduate Medical School in London (UK), where Iain Macintyre had recently co-discovered calcitonin, and the mechanism of action of this hormone was unknown. I set up a method for urinary hydroxyproline assay when I arrived there, and decided to see whether its release from bone was affected by calcitonin in the rat. That provided evidence suggesting that calcitonin inhibits bone resorption and established the interest in calcium metabolism and bone biology that has lasted since then. I then worked for the next 2 years with Dr Macintyre, who has been a great mentor of mine, before returning to Melbourne (Australia) and working for the next 3 years on parathyroid hormone (PTH) with the late Roger Melick, who was another greatly valued mentor.

Who have been your major influences in the field?

Iain Macintyre helped me greatly throughout my career, and Roger Melick continued as a colleague and source of support for the years until I left Melbourne for Sheffield (UK) in 1974. Several colleagues outside my own research group have influenced me greatly over many years. The most prominent among these have been the late Gideon Rodan (first at the University of Connecticut, CT, USA, then at Merck, NJ, USA), with whom I was fortunate to share many discussions regarding bone biology and the cells of bone, which often seemed at first to be taking us along unlikely paths, but gave us experiments to plan and concepts to try and prove. Larry Raisz (University of Connecticut), Steve Krane (Massachusetts General Hospital, Harvard, MA, USA) and Armen Tashjian (Harvard), Graham Russell (Sheffield and Oxford, UK) and the late Herbert Fleisch (Davos, Bern and Lausanne, Switzerland) are others with whom I shared greatly valued intellectual exchange over decades. One with whom I have worked closely and productively for approximately 30 years, while both of us were often fairly competitive about it, is Greg Mundy (Rochester [MN, USA], San Antonio [TX, USA] and Nashville [TN, USA]).

The most important influences, though, are those of a succession of wonderful people that worked with me for varying lengths of time over those years. There are too may to name, but just a selection include John Eisman, Jane Moseley, Nicola Partridge, Matthew Gillespie, Julian Quinn and Natalie Sims, spanning over 36 years.

What are your abiding memories of your time in Sheffield?

I remember Sheffield as simply a wonderful place to work. I went as a Chair of Chemical Pathology, but had no routine commitments, so I had a mandate to establish research in what were new laboratories in the Hallamshire Hospital. In doing that I was able to work in the laboratory myself much of the time, and had the benefit of great help from a young colleague who came from Melbourne with me to help establish the Department (Valdo

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Michelangeli), as well as an outstanding post-doc, Nick Hunt. I received great support from the Dean at Sheffield, the late Bill Crane (Professor of Pathology), and rapidly found that I was able to collaborate very productively with fine pathologists, one of whom, James Underwood, helped us to study morphology alongside biochemistry in the investigation of human cancers, as well as in the rat osteogenic sarcoma, which we induced.

We were able to begin an interest in metabolic bone disease in Sheffield, setting up the first such clinic in cooperation with the orthopedic surgeons Tom Duckworth and Tom Smith. This took off particularly well when I was able to recruit Graham Russell to Sheffield, which was a highlight of my time there. When I left to return to Melbourne after 3½ years, to my great delight, and to Sheffield's benefit, Russell was appointed as the Chair, and over the ensuing years established Sheffield as a leading center for the study of bone disease, before he left for Oxford in 2001.

Did your time as Director of St Vincent's still allow you to spend time at the bench? If not, did you miss day-to-day research?

I really had very little time for work at the bench when I was Director of St Vincent's Institute – in fact, this restriction had started a few years before that, and it was always a matter of regret to me because I knew that I was never happier at work than when working in the laboratory. Whenever the opportunity presented itself, I would happily help out in the laboratory – increasingly as 'unskilled labor' though. However, what I always did was to make sure that I engaged in day-to-day discussion of experimental work, planning and evaluation of original data.

What impact did your identification & characterization of PTHrP have on your own research focus, & the field as a whole?

The discovery of PTH-related protein (PTHrP) had a big influence on the direction of research. It came after I had been interested in the skeletal complications of cancer for almost 20 years – an interest that Roger Melick and I shared when I worked with him from 1967. As soon as the structure of PTHrP came before us, it was obvious that this protein would have interesting effects that could lead us anywhere, and from the outset it seemed to us that the evolutionary origin of PTHrP was likely to be very early.

Within less than a year we found that PTHrP was produced in many tissues of the body, beginning with skin, but, particularly, we were able to show, with Tony Care (Leeds, UK) and Ivan Caple (Melbourne), that PTHrP, while not acting as a hormone postnatally, does so in the fetus, where we found that in sheep it promotes calcium transport across the placenta from mother to fetus, making it available for the growing fetal skeleton. When we found that PTHrP was produced very commonly in breast cancers, that set us out upon research that has lasted to the present day, establishing the role of cancer-derived PTHrP in the development and progression of bone metastases, particularly in breast cancer.

There is no doubt that PTHrP had a great impact on the field of bone research, and indeed other areas, due to its multifunctional role in many tissues.

Have you noticed a change in the public's perception of cancer during your career? What impact has this had on your research?

I suppose the main thing I note from my association with cancer research is that the public expects early diagnosis, having come to realize how this can benefit treatment and prognosis. That is particularly so in breast cancer, where widespread availability of mammography in screening has led to the detection of smaller cancers and, therefore, better prognosis. This is something that became obvious to us in a prospective clinical study of breast cancer that we began with my surgeon colleague, Michael Henderson (Melbourne), in 1989, and have continued for 17 years. The aim was to relate PTHrP production in primary breast cancer to the later development of skeletal complications, particularly bone metastases. By the mid-1990s it became obvious that tumors were significantly smaller, and as the years have gone by, the incidence of skeletal complications in patients who have undergone breast cancer surgery has decreased quite markedly. This is obviously good for patients cared for under such a system, but it does mean that clinical studies with skeletal events as an outcome now need to include very large numbers of patients.

What are your thoughts on the recent controversy surrounding bisphosphonates & osteonecrosis of the jaw?

We need to understand its mechanism much better than we do currently. Is it the direct result of profound blockade of bone turnover, preventing

the bone's repair capacity? If it is, we might expect it to be associated with resorption inhibition other than by bisphosphonates. I do not know the answer to this. It certainly appears to be sufficiently uncommon in osteoporotics treated with bisphosphonates so that it should not provide a contraindication to their use in patients who can benefit from them.

How do you see the field developing in the postgenomic era?

Genome-wide analyses will allow the genetic epidemiologists to show us the wide range of genes that can contribute to bone fragility. It will require better means of clinical evaluation than we have now though – bone mineral density measurement is not good enough – but we will need new approaches in imaging that will allow us to assess bone quality. The genetic information, in conjunction with these latter methods, will also allow us to eventually tailor treatment to individual patient's requirements.

What has your most recent research focused on & where is it heading in the next few years?

My most recent and current interest is in finding out the details of intercellular communication processes in bone that result in the coupling of bone formation to resorption. In particular, what we are seeking is products of the osteoclast itself that contribute to bone formation in the bone-remodeling process. The pursuit of this does not exclude a contribution from growth-promoting factors resorbed from the bone matrix, but specifically seeks an osteoclast product that can be released independently of the resorptive function of the osteoclast.

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