TOM REEVE ORATION AWARD

A FORTUNATE LIFE

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I have never felt like I was tied down to any one place or any one job. I have had a good life…I have been very fortunate and I am thrilled by it when I look back.

AB Facey, *'A Fortunate Life',* 1981

It was truly a red letter day in my life when David Goldstein phoned to say that I would be this year's Tom Reeve Oration Award recipient. This emotion flowed not only from the honour of having the award bestowed upon me by my peers in the Clinical Oncological Society of Australia (COSA), but also because of the great respect and admiration I have for both Tom Reeve as an individual and for COSA as a society.

Tom became one of my professional heroes by virtue of his achievements in bringing discipline and structure to the provision of cancer services in Australia through the Australian Cancer Network (ACN). As all who have worked with him know very well, he has a remarkable ability to harness the efforts of disparate individuals and craft groups, and to keep them working. The ACN guidelines produced under his stewardship are testimony to this ability, culminating today in the release of the latest edition of *Guidelines for Melanoma,* which has already received international recognition as an evidence-based framework for a non-prescriptive but counter ad hoc approach to patient management.

But there is more to Tom than cancer guidelines and I would encourage everyone here to read his piece *Following Fortune's Path,*[1] which summarises his life experiences and how they molded his philosophy. The lesson here for young oncologists, that I can also endorse, is to keep one's options open and to grasp opportunities as they arise.

My association with COSA dates back to the late 1970s when the society was still in its formative first decade. The concept of a multi-disciplinary disease (rather than craft) focused society was truly visionary and I was privileged to work with two of the founding fathers and early presidents of COSA, Leicester Atkinson and Bob Melville. This was also the time when the Warramirri people consented to the use of the Marryalyan as the official emblem of COSA, symbolising as it does, the realisation of truth through discussion and argument. The gold Marryalyan that comes with the Tom Reeve Award is indeed very special in this context.

A fortunate life

I entitled my address "A Fortunate Life" (with apologies to AB Facey) because whatever I have achieved is the result of my good fortune in having a series of great opportunities come my way, being at the right place at the right time to take up those opportunities and having the support and encouragement of my parents and nuclear family to pursue them.

Opportunity 1: education and training

My first great opportunity, as the son of parents who had no educational opportunity, was to go to medical school in Queensland with the support of Commonwealth and State scholarships. During my time in medical school, I became fascinated with cancer and resolved to devote my career to its study. After graduation and internship, I embarked on specialty training in radiation oncology (in those days "radiotherapy") which was the only medical discipline devoted to cancer. My training at the then Queensland Radium Institute was influenced by inspirational teachers like Kevin Mead, Bruce Kynaston and Nobby Bourne who not only gave me a good clinical foundation for practice, but also encouraged my urge to do research.

Opportunity 2: fellowship to the Gray Laboratory

The visit to Queensland in 1971 by Dr Tikvah Alper, a research scientist from the Hammersmith Hospital, was the catalyst for my research career. Tikvah was a radiobiologist whose most notable, but largely unrecognised insight, stemmed from her studies of the radiation dose response of the agent responsible for propagation of the spongiform encephalopathy called "scrapie" in sheep. Using radiation target theory, she calculated that the infectious agent must be smaller than any known virus and therefore could not be nucleic acid based. This was long before prions were recognised or named.

In any event, I managed to convince Tikvah of my desire to pursue research and she undertook to arrange a fellowship for me at the Gray Laboratory at the Mt Vernon Hospital in Northwood, Middx, on the outskirts of London. The Gray Laboratory was named for Hal Gray and was perhaps the most famous radiobiology facility in the world at that time. This offer was particularly attractive

to me as my trail-blazing forebear and role model from Queensland, Rod Withers, had gone to the Gray Lab 10 years earlier. My fellowship was funded by the then British Empire Cancer Campaign and although I received only a subsistence salary of £1800 per annum, it was perhaps the best career move I ever made.

My wife, Desley, and I arrived in London in February 1972 in the middle of a freezing winter compounded by the great coal miners' strike. I was assigned to work with Harold Hewitt, an experimental pathologist who had become famous by producing the world's first in vivo radiation cell survival curve for a murine leukaemia. However, his real interest was in transplantation biology and he gave me the project of investigating the mechanism whereby the transplantation of living tumour cells from one mouse to another was facilitated by a mixture of lethally irradiated cells. This proved to be an enormously challenging project with an intellectually satisfying outcome – the lethally irradiated cells acted as a thromboplastic nidus at the transplantation site. I still count the paper[2] that I wrote under Harold's guidance reporting these results as one of my best, and it attracted some international attention in the context of metastasis formation.

Harold Hewitt's influence on my scientific philosophy was great. A disciple of Karl Popper, he admonished me never to become so emotionally involved in an experiment as to be "disappointed" if the result disproved the underlying hypothesis, or worse, to try to force the data into being "consistent" with the hypothesis. After completing my fellowship with Harold, I spent another year with Jack Fowler on more classical radiobiology related to fractionation effects in normal tissues and tumours, a subject that would figure large in later years in my work with Rod Withers.

Opportunity 3: faculty position at M D Anderson

By 1976, it was obvious that I had educated myself out of a job in Australia if I wanted to pursue radiobiological research. I was extremely fortunate to receive the offer of a faculty position in the Department of Experimental Radiotherapy at M D Anderson Cancer Centre. The chairman of this department, Herman Suit, had just left to take up a new position at Harvard and Rod Withers was left in charge. He organised for me to have a 50/50 split of my time between the lab and the clinic, where I came to work with the legendary Gilbert Fletcher, one of the three founding fathers of American radiation oncology. My clinical responsibilities were circumscribed and focused on fast neutron therapy trials and the use of TBI in the conditioning regimen for bone marrow transplantation. I had argued on radiobiologic grounds that fractionated TBI would yield a better therapeutic ratio than the single dose normally used, and I implemented this regimen at M D Anderson, working with haematologist, Karl Dicke. On the fast neutron front, I worked with David Hussey on the Phase II trials that would ultimately lead to formal testing of fast neutron therapy in the 1980s. I also became involved with the head and neck service, which provided the direction for my future clinical specialisation in this area.

In the lab, I worked with Bill McBride and later Luka Milas on non-specific immunological factors affecting tumour transplantation and with Rod Withers and Howard Thames on analysis of the fractionation effects of radiation on normal and neoplastic tissues. This led to the discovery of a systematic difference in fractionation dependence between acutely reacting and late reacting tissues, and the later publication of one of our most highly cited papers[3] describing a new isoeffect formula for change in dose per fraction.

Opportunity 4: Head of Radiation Oncology at M D Anderson

In 1979, I returned to Australia to the Institute of Radiotherapy at the Prince of Wales Hospital (where I first became involved with COSA), but I had been there only two years when Gilbert Fletcher retired and I was approached by the search committee for his successor to be a candidate. My wife and I thought long and hard about this but finally decided to give it a go, and much to our surprise, I was offered the position. In deciding to commit long-term to Houston, I was influenced not only by the fantastic research environment it provided, but also the chance to work in a clinical practice environment that to my mind, is the model for an integrated cancer centre; all the medical staff are full-time employees organised into disease and/or site specific multidisciplinary teams. There is a single practice plan for all the professional staff (medical and research), which means that there is no financial incentive for any group to recommend a particular plan or modality of treatment. The hospital is state-owned, but is autonomously governed with the proviso that it contracts to treat all Texans with cancer regardless of their ability to pay. This encouragement of entrepreneurship along with social responsibility works extremely well and has resulted in M D Anderson becoming one of the world's greatest cancer centres. It is certainly a model that has great appeal when compared to the bureaucratic constraints on growth that we face in the public hospital systems of Australia.

As head of radiation oncology, I had much less direct involvement in laboratory research than previously, but I did participate in a number of very productive collaborations with Bill Brock and Fady Geara (predictive assays of radiation response), and Luka Milas and Kathy Mason (integration of radiotherapy with chemotherapy and biologicals). On the clinical side, I was principal investigator on the Fast Neutron Therapy Phase III trials, which showed if anything, a worse therapeutic ratio than could be achieved with photons. (There is a lesson here for proponents of charged particle therapy.) I also continued work with Rod Withers and later Kian Ang on developing new radiobiologically-based fractionation schedules, which were subsequently exported to the Radiation Therapy Oncology Group for formal evaluation. My clinical focus was on head and neck cancer, where I worked closely with Helmuth Goepfert and Ki Hong on protocols aimed at organ preservation and strategies to avoid unnecessary or futile treatments. I was also involved with Charles Balch on a Phase II trial to investigate the use of hypofractionated radiotherapy as an adjuvant in high risk melanomas.

This intramural activity was complemented by my involvement at a number of levels in the National Cancer

Institute and with various professional organisations, in particular the American Society for Therapeutic Radiology and Oncology and the American Board of Radiology (ABR), which has the responsibility for certifying the competence of American trained radiologists and radiation oncologists. Perhaps my most significant achievement on the ABR was to lead the push for time-limited certification with the requirement that all radiation oncologists should undergo re-certification every 10 years. As President-elect of the ABR, my obligatory resignation to take up my next major opportunity was my greatest regret in leaving the US.

Opportunity 5: Professor-Director of Radiation Oncology at Peter MacCallum Cancer Centre

The last great opportunity of my professional life came when, in 1994, I was offered the position of Professor-Director of Radiation Oncology at the Peter MacCallum Cancer Centre in Melbourne. Peter Mac was at that time in the throes of reformation under the leadership of its visionary CEO, Dr John Morris. Having succeeded in getting a new facility for Peter Mac built in East Melbourne, John set about recruiting academic leadership in cancer research and each of the clinical disciplines of oncology, with the support and encouragement of a vital board and philanthropic donor base. I arrived in 1995, just after Joe Sambrook, who had come to head the research division. Over the next few years, we were followed by John Zalcberg (medical oncology), Bob Thomas (surgical oncology) and Sanchia Aranda (nursing oncology). Another key early recruit was Rod Hicks, who set up Peter Mac's now world recognised metabolic imaging centre. I found to my delight that the existing medical staff at Peter Mac were enthusiastic about embracing a mode of practice broadly based on M D Anderson's with a research focus driving clinical excellence. Integrated multidisciplinary care, based on disease type/site units, was accepted as the mantra of Peter Mac. At the same time, the academic output of Peter Mac, measured in terms of grants, publications, initiation of clinical trials and number of trainees and graduate students, increased rapidly. This profile attracted support from industry for us to participate in the development of new technologies like PET and later PET/CT and IMRT, as well as to be involved in early stage trials of new drugs and biologicals.

Unfortunately, the halcyon days of the late 1990s were cut short by political winds of misfortune which saw Peter Mac lose its independence for several years, and then, without its visionary CEO, to be re-constituted as a much less entrepreneurial organisation. Under these circumstances, I stepped down as Professor-Director of Radiation Oncology in 2002, but stayed on the staff in a part-time clinical research capacity and also took on the challenge to set up a foundation to support the work of Peter Mac.

Outside of Peter Mac, since returning to Australia, I have been closely involved with the Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists and have had the good fortune to work with two outstanding leaders, Liz Kenny and Roger Allison, who between them have done so much to improve the quality of radiation oncology services and professional competence in Australia.

I have also had the great pleasure of seeing the Trans Tasman Radiation Oncology Group (TROG) blossom into a world class clinical trials organisation under the leadership first of Jim Denham, then David Ball (in whose tenure as President a fully funded trials headquarters was established), and most recently Bryan Burmeister. The success of TROG and the high level of participation of Australian and New Zealand radiation oncologists in clinical research bode well for the future of our discipline as one pillar of coordinated cancer care.

Closing remarks

There is no question that the quality of cancer services in Australia has improved significantly over the past two decades; and this improvement is now evident as a measurable decrease in cancer mortality. While a commitment to research is essential to continuing this improvement, we should never under-estimate the value of doing well what we already know how to do. This is nicely exemplified by the results of a recent international trial, "HeadSTART", on which I was co-PI with Danny Rischin. The trial was designed to test the value of adding an hypoxic cell cytotoxin to standard cisplatin based chemoradiotherapy for advanced head and neck cancer. The results of the trial however, showed that any improvement attributable to the new drug was overwhelmed by the effect of protocol deviations in radiation therapy planning and execution – patients treated according to protocol had a disease-free survival nearly double that of patients with unacceptable deviations.

The importance of doing well what we already know is a very fitting way to end this address, reinforcing as it does, the critical role of cancer treatment guidelines and the contribution of Tom Reeve to their development.

Last and most importantly, I want to thank those who nominated me for this award and to acknowledge the love, support and encouragement I have received from my wife and daughters, Kirstie and Lexi, throughout my career. Without them, there would be no meaning to a successful professional life.

References

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