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John Violet: radiation oncologist and physician scientist who pioneered targeted radionuclide therapy for prostate cancer

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In every hospital—every lucky one, that is—there is a doctor who has a reputation for staying late to talk with patients, giving them as much information and time as they need to absorb and understand their diagnosis and treatment options. At the Peter MacCallum Cancer Centre in Melbourne, Australia, the radiation oncologist John Violet was that doctor. Violet was known as much for his empathy as his tireless quest to develop a new generation of tailored cancer treatments and his profound respect for the autonomy of patients he recruited into trials.

There was also more than a whiff of the Renaissance man about him. An acclaimed photographer with a love of cityscapes, he came to work dressed in purple three piece suits, with a fountain pen and leather briefcase, carrying off what one of his colleagues called a “slightly bonkers magician fashion look” with aplomb. He was an avid traveller, a connoisseur of food, wine, interior design, and 1980s rock music, and a devoted father who was at his happiest when singing along to Queen to the delight of his two young daughters.

Violet was just three years old when his father—a beloved British general practitioner who worked on the Orkney Islands—died of an astrocytoma, a loss that fuelled Violet’s drive to discover better cancer treatments. An obituary in *The BMJ* of Violet’s father noted that his “interest in his patients went far beyond their medical problems,” a description that applied equally to Violet himself. Violet and his two sisters—Mary, a nurse, and Julie, who works in the humanitarian sector—were also inspired to join caring professions by their mother, a nurse from Ghana, and their Irish born grandfather, who trained in tropical medicine and spent his life working in Ghana, serving as personal physician to President Kwame Nkrumah.

If there was a thread that bound together the passions and phases of his career that took him from London to Wellington, New Zealand, and finally Melbourne, it was Violet’s push to keep trying innovative methods, thinking outside the box in matching the right approach to the right patient. “His mindset,” said John Buscombe, president of the British Nuclear Medicine Society and Violet’s research colleague at the Royal Free Hospital in London, “was to ask, ‘how can we be doing better than we’re doing now?’” Violet’s motto, said Buscombe, was “to treat each patient as an individual and individualise their treatment.”

Targeted treatment

In conventional chemotherapy or radiotherapy, any patient with the same kind of tumour receives the same treatment. For Violet, the appeal of new targeted approaches was their potential not just for greater effectiveness, but for fewer side effects. His search for treatment individualisation led to his becoming a pioneer in the use of radionuclides for both cancer therapy and diagnostics, an emerging field called “theronostics.”^{1 2}

His interest in radionuclide therapy began at the Royal Marsden Hospital in London, when he worked as a senior registrar with Clive Harmer, consultant clinical oncologist, treating patients with thyroid cancer using radioiodine. He then became a clinical research fellow in the Cancer Research UK targeting and imaging group at the Royal Free and University College London (UCL) Medical School, where he studied radioimmunotherapy—the use of tumour specific antibodies to target radionuclides to cancer cells—for lymphoma and colorectal cancer.

His research, said Richard Begent, emeritus professor of oncology at UCL, helped tackle several critical questions. For example, the radiolabelled antibodies that Violet was studying were known to

persist in the circulation for several days, bringing into question whether or not the treatment should be given in spaced doses (fractionation). “His laboratory studies with Barbara Pedley,” said Begent, “showed that the most effective therapy within safe limits was achieved with a single high dose rather than a fractionated regimen, an important finding for the design of clinical trials.”³

Violet worked with colleagues to develop new approaches to treating lymphomas, sorely needed given that some patients develop drug resistance. He helped develop and run the first clinical trial of radioimmunotherapy with a chimeric mouse-human antibody directed against a receptor called CD25, a target commonly found in Hodgkin and T cell lymphoma.⁴ “This showed a high level of responses,” said Begent, “and also permitted development of a sophisticated system of dosimetry based on gamma camera imaging and physiological measurements.”

Legacy

But it was at the Peter MacCallum Cancer Centre, which Violet joined 10 years ago, where he made arguably his most important scientific contributions. Collaborating with Michael Hofman, a nuclear medicine physician, Violet began studying the use of a small radioactive molecule (177Lu-PSMA-617) to treat men with prostate cancer whose disease had progressed after standard treatments. Hofman and Violet co-led a phase II clinical trial of this molecule, recruiting 50 men with prostate cancer, that found high response rates, low toxicity, and improved quality of life; the original trial report has become one of the most widely cited and influential papers in the subject.⁵⁻⁷ Novartis purchased the rights to this molecule and is conducting a phase III trial, with the hope that the treatment will be licensed next year. “This will be his legacy,” said Hofman. “It will live on beyond him.”

“In a career cut so tragically short, it is a rare and remarkable achievement to have sustained and developed a complex scientific theme collaborating with many colleagues,” said Begent. “His work has the potential to benefit thousands of patients around the world and all achieved while also practising as a clinical oncologist warmly valued by his many patients and colleagues.”

Violet leaves his former partner, Jo Violet, a child and adolescent psychoanalytic psychotherapist and adult Jungian analyst in Melbourne, and daughters Imogen and Mia.

John Violet (b 1969; q Royal Free Hospital Medical School, London, 1993), died on 5 October 2020. The cause of death is unknown

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