

IN MEMORIAM



Prof. G. Barry Pierce (1925-2015)



Gordon Barry Pierce, my great mentor and long-time friend died in November 2015 at the age of 90 years. We will all miss him. What we are left with, however, are reminiscences of moments we spent with him, his jokes and stories to be retold and passed along, tidbits of advice, and pearls of his common-sense Canadian wisdom. A vision of a better world to which he contributed so much. Scientific contributions too numerous to list, many of which had major impact on us who were interested in the same problems as he was. Seminal discoveries that impacted the progress in several fields of scientific endeavor. Major new concepts of oncology and developmental biology that opened new vistas and revolutionized our thinking about the crucial problems of biology and medicine. Unforgettable seminars and lectures. Unquenchable love for science. And much more that, nevertheless, can be summarized in two wondrous exclamations: What a man! What a life!

G. Barry Pierce was born as a Canadian citizen on July 21, 1925 in Westlock, Alberta. Biographical details about his Canadian Army service in World War II, his education at the University of Alberta and his subsequent years in Academia were briefly reviewed in the preamble to the 1991 interview that Barry gave to the Editor of this journal, *The International Journal of Developmental Biology*, Juan Aréchaga (Aréchaga, 1993). The interview, which contains numerous other details about Barry's long and productive life was included in the G. Barry Pierce *Festschrift* appropriately entitled *Developmental Aspects of Neoplasia* (Damjanov and Martínez-Hernández, 1993). His life story could not be retold better than he did it himself; Juan recorded it for posterity. At the end of this interview one may also find the key references to Barry's work. This *Festschrift* also contains other articles by his friends or students and colleagues.

Anybody and all those who are interested in the fascinating life of G.B. Pierce may be advised to visit the online *Festschrift* (<http://www.intjdevbiol.com/web/issues/contents/vol/37/issue/1>). It would be superfluous for me to repeat all that Barry said some 20 plus years ago, but for the historians of science, that volume of the *Int. J. Dev. Biol.* is a treasure-trove of biographical facts, which cannot be found anywhere else. Likewise in it one can find the complete list of Barry's awards, honors and distinctions and the description of the main milestones of his scientific life. For the record, let me just list the most important honors: American Cancer Society Career Professorship; the McFarlane Visiting Professor of Medicine, University of Glasgow; Doctor Honoris Causa, University of Granada, Spain; Distinguished Professor, University of Colorado Health Sciences; the Rous-Whipple and the Gold Headed Cane Award from the American Association of Pathologists.

By education and formal training Barry was a medical doctor and a pathologist. By avocation he was however an iconoclastic scientist who could not be readily classified. In addition to microscopy needed for his pathology studies early in his scientific career, he branched out into experimental biology, embryology, biochemistry, and immunology. This multidisciplinary approach reflected his creativity but at the same time opened new seascapes that were never explored before. Barry's imagination knew no limits; combined with visionary problem solving skills, it conceptualized ideas that were not only ground breaking, but also radically fresh and *avant-garde*, far ahead of his own times. The notion of cancer as a caricature of normal development, the idea that a single cancer stem cell can give rise to multicellular tumors, and the supposition that tumor stem cells could differentiate and lose their malignancy, were not only conceived in Barry's lab, but were also experimentally proven and expanded. The basic tenets of differentiation therapy were laid down several decades before they were translated into practice and applied in clinical medicine. Major technological breakthroughs revolutionized immunohistochemistry and made it clinically relevant. Modern pathology would not have become what it is today were it not for the pivotal innovations made in the 1960ies by G.B. Pierce and his collaborators.

Persistence and pursuit of ideas which he though were important was one of the main hallmarks of Barry's scientific work. In this context let's take just one example, his work on teratomas and teratocarcinomas. In the 1950ies and 1960ies, who would have ever thought that the study of teratoid tumors of the mouse would ever give any significant yields? Yet Barry persisted in his investigations of those "clinically unimportant tumors" (as some funding agency pundits referred to his research model), exchanging notes

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and data with yet another teratoma scientist, Leroy C. Stevens. Decades of work ultimately began paying off huge dividends and the entire field was given prominence by the Nobel prize awarded to three scientists, who could be considered as legitimate heirs of Pierce and Stevens. Their teratoma/teratocarcinoma work enabled them to isolate embryonal carcinoma cells, the malignant stem cells of teratocarcinomas, which ushered the era of tumor stem cell biology. Embryonal carcinomas could be induced to differentiate into somatic cells, enabling scientists like Ralph Brinster and Beatrice Mintz to construct tumor-derived embryos and produce live mice, expressing tumor genes. Embryonic stem cells were developed *in vitro* as equivalents of teratocarcinoma stem cells. These developments enabled researchers to construct transgenic mice, and develop ingenious techniques of modern bioengineering. In 1990, Jamie Thomson isolated human embryonic stem cells. In retrospect, one cannot but wonder if all this would have ever occurred without the visionary work on the murine teratoma/teratocarcinoma, which turned out to be a biological *Rosetta stone*, linking embryonic and neoplastic development.

Barry had an incredible sense for choosing winning projects and for identifying potentially important research areas. He clearly saw the jewels among the pebbles along the road on which all of us have been walking. Let just take the example of parietal yolk sac carcinoma, which he identified as a potential source for mass production of basement membrane components (Pierce *et al.*, 1962). How many biochemists and later molecular biologists profited from Barry's discovery of that basement membrane producing tumor?

Barry had a knack for spotting talent and attracting young people to work with him. One of these, a medical student by the name of Lewis Kleinsmith isolated 1,700 single cells from teratocarcinoma derived embryoid bodies and transplanted each of them in an attempt to prove that he could grow all the tissue of teratocarcinoma from a single tumor cell (Kleinsmith and Pierce, 1964). In his Nobel Prize acceptance oration (2007), Sir Martin Evans named it as the single most important paper documenting the existence of pluripotent tumor stem cells. Would that herculean and ground-braking paper ever have come into existence, were it not for Barry's talent to spot a potential winner, a student with a sparkle in his eyes, whom he persuaded to join his lab?

Barry shared his own ideas unselfishly with others. He also knew how to profit from the ideas developed by other scientists, learn new techniques from them and assemble winning multidisciplinary teams. His long term collaboration with Leroy C. Stevens, who gave him some of his murine teratocarcinomas is just an inspiring example. Also long-term projects with Paul Nakane, A. Reese Midgley, and J. Sri Ram established the foundations of modern immunohistochemistry and made it applicable to clinical diagnostic histopathology (Midgley and Pierce, 1962; Sri Ram *et al.*, 1963; Nakane and Pierce, 1967). His pioneering work on the heterotransplantation of testicular tumors into immunosuppressed hamsters, which he started with Frank Dixon taught us a lot about tumor stem cells and ultimately led to the isolation and *in vitro* culture of human embryonal carcinoma cells and their normal equivalents, the human embryonic stem cells (Andrews, 2002)

Barry was a great teacher and he liked to talk about his research, about his innovative ideas and new projects. I still remember his musings on how one could stimulate students to become creative scientists or dedicated physicians. It helped that he was a great story teller. He also had a wonderful and sharp sense of humor and he could entertain students for long periods of time without interruption. The same applied to entertaining his colleagues long into the night. Students of all ages loved him, in part because he loved them as well.

As a transplant from Europe, I would be remiss for not including a few lines about Barry's generosity to many of us from the other side of the Great Pond. As a Canadian who enjoyed the hospitality of the US throughout his life, he probably felt that other newcomers deserve to be welcome the same way as he was. Barry's lab was always open to scientists from abroad, and many Europeans flocked to Denver to learn various techniques and test their own ideas in discussions with him. Some of them like Francisco (Paco) Nogales, Fred Bosman, or Juan Arechaga are still active holding prominent positions in European Universities, thus continuing Barry's life-time mission and devotion to science. He was especially kind and generous to my old Croatian professor Nikola Skreb, and by extension to his students Davor Solter and myself. After I emigrated to the US, Barry helped me start my research laboratory and were it not for him, I doubt that I would have ever gotten even my first NIH RO1 grant. I was one of the lucky ones whom he promoted and supported, even though I often wondered why. When Barry stepped down as the North American Editor of the journal *Differentiation*, he nominated me for that job. I am not sure how much I added to that journal; however, Barry's contributions to launching and later transforming *Differentiation* into a respectable biomedical journal should not be forgotten. I see it as part of his educational function and a long term effort and commitment to promoting science at all levels, preaching to as many audiences as possible. Biomedical science has had few champions like G. Barry Pierce. He remained devoted to science his entire life.

Barry liked to make points by using unusual words, some of which he invented himself. Some of these words would not be considered politically correct or printable today. One of his favorite neologisms was the word "yes-butlers". He liked to use it for opponents and sceptics not willing to accept his ideas. It was a term for people who would say "yes, yes" and then end the discourse by killing the

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proposal with a final sentence beginning with “Yes-but”. Barry taught us not to accept a "yes" if it were followed by a "but". In the spirit of his enduring legacy let me thus finish this *In memoriam* the way I think that Barry would have approved:

A great man has died, yes, but we must continue along the pathways he led us. Despite all the yes-butters!

Ivan Damjanov
Kansas City, Kansas, USA, January, 2016

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