

Kurt Hellman – a rare breed of medical and scientific humanitarian



Kurt Hellman

(May 12, 1922 April 2, 2013)

Driven by a desire to know what is beyond the horizon led the UK clinician and pharmacologist Kurt Hellmann to discovery of the unique cytotoxic, cytoprotective and antimetastatic activities of bisdioxopiperazines in his laboratory at ICRF's Cancer Chemotherapy Unit in London in the early 1970's. Following Karrer, Goldin and Humphrey's description of the Lewis lung (3LL) carcinoma as a model for metastases, Hellmann set up 3LL as a screen for antimetastatic compounds in 1968. The first compound to be tested in this antimetastatic drug screen was the cytostatic agent DL-razoxane (ICRF-159). As serendipity would have it, DL-razoxane showed almost total suppression of metastases without seeming to affect the growth of the primary implant, thus making DL-razoxane the first fully antimetastatic compound. This work was regarded as a major breakthrough when published in a landmark paper in the BMJ on March 4, 1972 (1). Hellmann clearly showed that a drug which normalised the tumour-induced pathologic vasculature prevented lethal metastasis. Such an observation pre-dated by many years the current interest in the conversion of tumour vasculature to a more normal morphology and function as a therapeutic approach (2), even in the emerging field of immuno-oncology (3). This biomedical discovery led Denys Wheatley further to muse on 'rediscovery in science' and ways, we might reduce the many claims of "new" discoveries that seem to be of considerable significance but are in fact rediscoveries (4).

By serendipitous coincidence of time and circumstances Hellmann had in the early seventies begun a collaboration with the US National Cancer Institute (NCI) to examine the unusual antitumour properties of this cyclised form of EDTA synthesised by the ICRF chemist, Andrew Creighton (5), when Eugene Herman working at Abraham Goldin's lab had independently discovered the cardioprotective effect of EDTA in his models. It was also found that DL-razoxane, and subsequently the less toxic but much more soluble D-razoxane (dexrazoxane, ICRF-187), was highly effective in preventing anthracycline-mediated cardiotoxicity and treating accidental anthracycline extravasation. The fascinating story can be found in the monograph edited by Hellmann and Rhomberg: "Razoxane and Dexrazoxane

- Two Multifunctional Agents" in 2011 (6). In the case of prevention of anthracycline cardiotoxicity by dexrazoxane Hellmann was driven by the desire what is beyond the barrier of the dose-limiting toxicity of anthracyclines. For doxorubicin with its broad spectrum of antitumour activity, as well as other anthracyclines, an irreversible, cumulative, destructive cardiomyopathy restricts full exploration of the antitumor effects of these drugs. The first demonstration of the cardioprotective effect of bisdioxopiperazines by classical pharmacology methods in the isolated dog heart was described by Herman in 1972 (7) the very year of Hellmann's BMJ publication on metastasis prevention! There was consistency of protective effect in all of the in-vivo animal species tested (8) which rapidly led to clinical trials in the US and in Europe in the early 1990's- first in adult breast cancer patients and subsequently in children with sarcoma and acute lymphoblastic leukaemia (ALL) (9).

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Currently dexrazoxane is the only FDA/EMA approved agent for preventing anthracycline cardiotoxicity which according to James Doroshow (NCI) should become an essential part as a protective agent in anthracycline-containing treatment schedules (10). In Circulation Research 29 March 2018, the pediatric cardiologist, Steven Lipshultz, responsible for many important primary and secondary prevention studies in cardio-oncology, published an update of the European Union label for dexrazoxane which, allows virtually all children to receive dexrazoxane starting with the first dose of anthracycline at the discretion of the treating provider without reducing its oncologic efficacy, even allowing safer anthracycline dose escalation' to keep the responders responding (11). In his JCO-editorial back in 1996 Kurt

Hellmann - with astonishing foresight - pointed out that pharmacological anthracycline cardiotoxicity prevention will increasingly become important for maintaining the quality of life of cured long-term survivors, especially for children with ALL whose cure rate now approaches 85-90%.

These two breakthroughs in translational metastasis research and ameliorating cancer drug toxicity are embedded in Kurt Hellmann's long life as a well-respected oncologist and researcher. He remained active as a writer, discussant, advisor and benefactor until the very end of his remarkable and productive life encouraging young investigators and giving them opportunities. His last letter to the editor of the Journal of Clinical Oncology was published just weeks before his death (12).

*As head of
Chemotherapy at
ICRF, he also had an
honorary professorship
in Radiotherapy at the
Westminster Hospital*

Kurt Hellmann was born in Nürnberg, Bavaria, on 12 May 1922, where he attended primary school from 1927 to 1932 and the first year of the 'Reformgymnasium' before having to emigrate as a 10-year-old boy with his parents and his elder brother to England in March 1933. On leaving school he worked as a lathe turner in a tool factory but, although this opened his eyes to the dismal home and working conditions of some of his workmates, which roused his socialist instincts, it didn't satisfy his intellectual curiosity. In the evenings he studied, well into the night, as an external student at Imperial College London and earned a B.Sc. in Chemistry. He accepted a post with a group at the MRC to help in a study of the effect of heat on men in various situations e.g. submarines. Initially due to go to Singapore, conditions dictated otherwise. The group was sent instead to the Anatomy Dept. at Oxford to work with Prof. Le Gros Clark. While there he met and made friends with Dr. Joe Weiner who was instrumental in debunking the authenticity of Piltdown Man. While in Oxford he did a D.Phil. in Pharmacology at Magdalen College (1953). Having learned about drugs he felt it was pointless not to know how they actually affected people. He therefore decided to do medicine. Because Magdalen had already got its full quota of medical students for the year he became a student at Balliol. As a student, financial assistance was gained by doing a few hours/week teaching mathematics to a ground crew at one of the USAF bases near Oxford – an amazing and amusing experience. He qualified B.M.ChB. in

1958. D.M. in 1964 with the prestigious Radcliffe Prize for Medical Research for his histochemical investigations on cholinesterase and amine oxidase in the skin. Having qualified he did both his medical and surgical pre-registration house jobs at the Radcliffe Infirmary and it was there during 1959 he met Jane who was doing a year as resident pathologist. At the end of July 1961 they were married at Chelsea Registry Office. He then joined Reckitt & Sons, Hull, to lead its Department of Pharmacology but was seconded to undertake medical research at the Department of Pharmacology, Royal College of Surgeons, London. In 1962 he became Director of the newly formed Department of Cancer Chemotherapy at the Imperial Cancer Research Fund London (ICRF; now the Cancer Research UK London Research Institute) - a post which he held until 1987. While head of Chemotherapy at I.C.R.F. he also had an honorary professorship at the Radiotherapy Dept. of the Westminster Hospital (now Imperial College) from 1972 to 1993. This was probably the most satisfying period of his life – combining research, seeing patients and working with colleagues, radiotherapist and surgeons whom he liked and for whom he had the greatest respect. Indeed it was a sad day when the Westminster Hospital closed.

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In March 1974, Kurt Hellmann founded with his co-editor Stephen Carter (Director of the Division of Cancer Treatment, US National Cancer Institute) the highly regarded journal 'Cancer Treatment Reviews' which he edited from volume 1(1), 1974 to volume 18(4) in December 1991. With Stephen Carter he published 'Chemotherapy of Cancer' in 1977 a convenient reference and guidebook for practising medical oncologists which ran through several editions. In March 1974 he organized the first meeting of the E.O.R.T.C. Metastasis Club which he founded together with Silvio Garattini, Director of the Mario Negri Institute for Pharmacological Research, Milan. In the early 1980s the ever-expanding interest in the field of metastasis led to the 'Metastasis Research Society'. Its first international meeting was organised by Kurt Hellmann

and Suzanne Eccles in London, in 1984 shortly after the inauguration of the Society's official journal 'Clinical & Experimental Metastasis' with Kurt Hellmann and co-editor Garth Nicolson.

In 1972 Kurt Hellmann acted as Chairman of the British Association of Cancer Research (BACR) and gave the 'Erasmus Wilson Lecture' of the Royal College of Surgeons. When the Queen opened a new wing at ICRF's Lincoln's Inn site in 1973 he was given the task of showing her around the Department of Cancer Chemotherapy in which she took great interest. Following the Royal visit he received an invitation to lunch at the Palace. Some 10 years later, as President of the Oncology Section of the Royal Society of Medicine, London, he was invited to give the 'Haddow Lecture' of BACR. Kurt Hellmann also made an memorable debut in 'A Career in Pharmacology' in 1961 filmed by members of staff of the Department of Pharmacology at the Royal College of Surgeons of England, then based at Examination Hall, Queen Square London, co-starring with the later Nobel Prize winner John Vane and others (13). The Wellcome Library also holds a recording of a 1993 interview between Kurt Hellmann and two other colleagues remembering Sir Stanford Cade (1895–1973). Cade was a pioneer in radiotherapy at the Westminster Hospital and an Air Vice Marshall of the Royal Airforce whose invaluable collection of case summaries was rescued by Hellmann upon the closure of the Westminster Hospital and given to the Contemporary Medical Archives Centre of the Wellcome Trust's Library (GC147). The published proceedings of 'The Stanford Cade Symposium' organized by Kurt Hellmann at the Royal Institution, London, in 1973 bear witness to his early interests in preserving our medical heritage.

As he grew older, Kurt Hellmann's socialist instinct became rather staunchly conservative. He was a great admirer of Churchill. In his younger days he had played tennis and squash quite well. He was interested in Oriental Art and classical music and he greatly admired the Arts & Craft movement and became a particular fan of the architect W.A.S. Benson, whose house in East Sussex was home for the last 35 years of his life. Kurt Hellmann died on 2 April 2013 at the age of 90 in Withyham, East Sussex, UK.

A fuller account of Professor Hellmann's life and career was published as a 90th birthday tribute in *Clinical & Experimental Metastasis* in 2012 (14). I would like to express my gratitude to Jane Hellman for contributions and memories.

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[N.B. Oncology News will in future include articles on people who have made significant contributions to our understanding on the disease and its treatment. While there have been hundreds, many of whom have been particularly outstanding (e.g. Charles Huggins received a Nobel Prize in 1967), we will try to feature those whom you (our readers) would like to portray. To submit, please send entries to editor@oncologynews.biz]