

Hormone therapy: a revolution in understanding prostate cancer

Manit Arya, Iqbal S Shergill, Philippe Grange, Mark Emberton

Lancet Oncol 2008; 9: 1112
University College Hospital, London, UK (M Arya FRCS, I S Shergill FRCS, M Emberton FRCS); and **Kings College Hospital, London, UK** (P Grange MD, M Arya)
 Correspondence to: Dr Mani Arya, Department of Urology, Institute of Urology, University College London Hospital, London WC1E 5DB, UK manit_arya@hotmail.com

Until the middle of the 20th century, little knowledge of the behaviour of prostate cancer existed and awareness of its exquisite sensitivity to hormones had not been realised. The conventional understanding was that prostate cancer was an autonomous, self-perpetuating, and fatal malignant disease, the progression of which could not be changed by external manipulation.

In 1941, Charles Brenton Huggins, a Canadian-born American surgeon, revolutionised our understanding of prostate cancer and irrevocably changed the approach of physicians in managing and researching the treatment of neoplastic disease in general. His pioneering work heralded the era of rational drug therapy for all cancers and earned Huggins the Nobel Prize in Physiology and Medicine in 1966.¹

Charles Huggins graduated from Harvard Medical School (Boston, MA, USA) in 1924. In 1927, he was appointed to the surgical faculty at the University of Chicago (Chicago, IL, USA) where he became Professor of Surgery in 1936. Subsequently, in 1966, he became the second surgeon to win a Nobel Prize in Medicine, with a comment from the Nobel Committee proclaiming Huggins' work had "already given many years of an active and useful life to patients with advanced cancer over the entire civilized world—patients who would have been lost to other forms of therapy".¹ Many have suggested that his ground-breaking discoveries, first published in 1941,² should have been acknowledged by the committee at a much earlier date.

In the original study by Huggins and Hodges² (his student), eight patients with metastatic disease to bone were selected from an initial group of 47 patients with prostate cancer. All eight patients underwent bilateral orchidectomy; however, before this procedure, five were started on daily injections of stilboestrol or oestradiol benzoate, and three were injected with daily testosterone

propionate. Serum acid-phosphatase concentrations decreased in patients who received oestrogen injection before the procedure and increased in those who received testosterone propionate. From these findings, Huggins and Hodges concluded that prostate cancer was receptive to androgenic activity in the body and that metastatic prostate cancer was inhibited by eliminating circulating androgens—either by surgical orchidectomy or by administration of oestrogens. Moreover, they also showed that prostate cancer was activated by androgen injections. These findings have provided the scientific basis for the contemporary treatment of prostate cancer.

For nearly 30 years after this seminal report by Huggins and Hodges,² patients with advanced prostatic carcinoma were managed either by surgical orchidectomy or oestrogens, until it was shown that treatment with oestrogens resulted in substantial thromboembolic and cardiovascular complications.³ This finding stimulated further research into alternative hormonal treatments, which culminated in the development of various antiandrogens (eg, cyproterone acetate and flutamide) and most notably synthetic luteinising-hormone-releasing-hormone (LHRH) agonists in the 1970s. The therapeutic effectiveness of LHRH in achieving medical castration has yet to be surpassed. Although these hormonal treatments were originally used to manage patients with metastatic disease, androgen ablation therapy is now used in a neoadjuvant or adjuvant setting in combination with surgery or radiation in patients with locally advanced disease only or in those with biochemical relapse after radical treatment for localised disease.

The epic work by Huggins and Hodges² will remain a cornerstone in the annals of medical literature because it initiated the use of endocrine therapy in the management of disseminated prostate cancer and showed that the course of neoplastic disease could be changed by rational external intervention. One can state with certainty that there are few articles in science, which have had, or will have, such a lasting impact.

Conflicts of interest

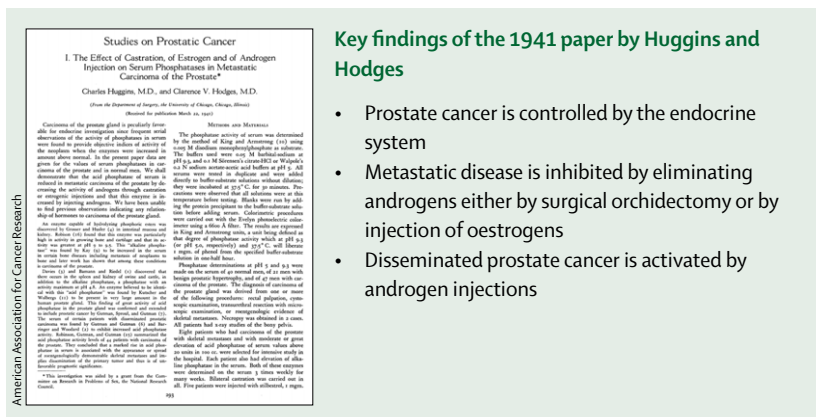
The authors declared no conflicts of interest.

References

- 1 The Nobel Prize in physiology or medicine 1966. http://nobelprize.org/nobel_prizes/medicine/laureates/1966/press.html (accessed Sept 22, 2008).
- 2 Huggins C, Hodges CV. Studies on prostate cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1: 293–97.
- 3 The Veterans Administration Co-operative Urological Research Group. Treatment and survival of patients with cancer of the prostate. *Surg Gynecol Obstet* 1967; 124: 1011–17.

Key findings of the 1941 paper by Huggins and Hodges

- Prostate cancer is controlled by the endocrine system
- Metastatic disease is inhibited by eliminating androgens either by surgical orchidectomy or by injection of oestrogens
- Disseminated prostate cancer is activated by androgen injections



American Association for Cancer Research