Commentary on Huggins and Hodges: "Studies on Prostatic Cancer"

William G. Nelson

See related article by Huggins and Hodges, Cancer Res 1941; 1:293–7.

"Studies on Prostatic Cancer: I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate," authored by Charles Huggins and Clarence V. Hodges (1) for the April 1941 issue of *Cancer Research*, may be the first translational research study of a molecularly targeted therapy in the history of cancer. Huggins earned a Nobel Prize in Physiology or Medicine in 1966 "for his discoveries concerning hormonal treatment of prostatic cancer." Today, 75 years after the publication of this classic *Cancer Research* article, androgen deprivation remains frontline treatment for advanced prostate cancer.

Prostate cancer mortality was greater than 25/100,000 in the United States in 1941 and remains a common cause of cancer-related death for men today (National Center for Health Statistics, Centers for Disease Control and Prevention). The prostate itself is a sex accessory gland present in all male mammals that contributes secretions to the ejaculate during intercourse. Normal growth, development, and differentiated function of the gland itself requires androgenic hormones; for most male mammals, lowering and circulating androgen levels by removal of the testes result in prostate involution. However, the hypothesis proffered in the article, that prostate cancers might in some way depend on androgens for malignant growth, had not been previously tested.

To understand whether prostate cancers might respond to the manipulation of sex steroid hormone levels, Huggins and Hodges employed a prescient tactic: the use of blood biomarkers of disease activity and of clinical benefit. To monitor disease activity in the serum of men with advanced prostate cancer, a colorimetric enzyme assay for a phosphatase with maximal activity at pH 4.8 was performed. Today, we know that this enzyme was prostatic acid phosphatase (PAP; also known as prostate-specific acid phosphatase or PSAP), which is produced by prostate epithelial cells for the ejaculate and is expressed by most prostatic carcinoma cells. Huggins and Hodges found acid phosphatase activity (likely reflecting PAP) to be elevated in serum specimens of 21 of 47 prostate cancer cases and 19 of 25 cases where bone metastases were present. For each of 8 men treated with castration, the elevated PAP levels fell precipitously, indicating androgen dependence of biomarker expression and underscoring an anticancer effect. Administration of testosterone to these men restored PAP to blood levels higher than before castration. PAP remained a valuable blood biomarker for prostate cancer until PSA was found to detect disease with a greater sensitivity more suitable for prostate cancer screening in the late 1980s (2). Supplanting serum PAP, serum PSA became an all-purpose prostate cancer biomarker, used now for disease risk stratification, for screening and early detection, for staging, and for disease monitoring. Nonetheless, assays for circulating PAP may still have uses, even in the PSA era. In a more recent study of 1,681 men with prostate cancer treated with radical prostatectomy, using other methods for detection of serum PAP, elevation of the biomarker was associated with a higher risk of disease recurrence after surgery (3).

To assess clinical benefit, a serum phosphatase maximally active at pH 9 to 9.5 was assayed. This alkaline phosphatase (ALP) was known to be produced by growing bone and cartilage (4), and had been found often elevated in cancers with bone metastases (5). Huggins and Hodges noticed that castration or estrogen administration tended to initially increase, and then to later decrease, ALP levels in men with metastatic prostate cancer. Commenting on the differential behavior of serum acid and alkaline phosphatases in men treated by androgen deprivation, they correctly attributed the ALP to osteoblastic activity resulting from tumor invasion of bone. Thus, using blood biomarkers, Huggins and Hodges were able to assert that androgen deprivation in men with metastatic prostate cancer both triggered an anticancer response and ameliorated cancer-associated disruptions in bone metabolism. Today, ALP is routinely measured throughout medical practice. Serum ALP elevations tend to indicate bile duct obstruction or osteoblast activity, including the osteoblast activity seen in metastatic prostate cancer.

The endocrine manipulations used to establish the androgen dependence of prostate cancers heralded the first androgen deprivation maneuvers quickly implemented to treat the disease. Testosterone is synthesized by Leydig cells in the testes upon stimulation by luteinizing hormone (LH). Dihydrotestosterone, a more potent androgen than testosterone, can be produced from testosterone by the action of 5α-reductases. Both testosterone and dihydrotestosterone bind to intracellular androgen receptors to activate the expression of target genes. Androgen deprivation therapy for prostate cancer involves lowering circulating testosterone to levels around or below 50 ng/mL. To reduce testosterone levels, Huggins and Hodges removed either of the testes, the major source of androgenic hormones in men, or injected estrogen, which can suppress the hypothalamic–gonadal axis to yield less LH. For the next four-and-a-half decades, the treatment of advanced prostate cancer involved the same two strategies: bilateral orchiectomy or estrogen administration. Pharmacologic doses of synthetic estrogens, such as diethylstilbestrol (DES), which provided dose-dependent suppression of testosterone to the castrate range, became a widely used "medical" alternative to surgical castration, even though commonly associated with additional side effects like the gynecomastia that were observed by Huggins and Hodges. A series of studies by the Veterans Administration Cooperative Urological Research Group ultimately revealed that although DES afforded a prostate cancer–specific survival rate equivalent to orchiectomy, men treated with high

Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland.

Corresponding Author: William G. Nelson, Johns Hopkins Kimmel Cancer Center, Suite 1100 Weinberg Building, 401 North Broadway Street, Baltimore, MD 21287. Phone: 410-955-8822; Fax: 410-955-6787; E-mail: bnelson@jhmi.edu

doi: 10.1158/0008-5472.CAN-15-3172

doses of DES suffered a high incidence of cardiovascular deaths (6, 7). In the 1980s, the introduction of the first LH releasing hormone (LHRH) analogue, leuprolide, spelled the beginning of the end of the castration and estrogen administration pioneered by Huggins and Hodges as the most common treatment approaches to advanced prostate cancer. A randomized trial comparing leuprolide to DES showed equivalent suppression of testosterone and dihydrotestosterone, but more gynecomastia, nausea and vomiting, edema, and thromboembolic events with DES, establishing LHRH analogues as the first-line androgen deprivation strategy for prostate cancer (8). Currently, a substantial arsenal of agents targeting androgen signaling is available for prostate cancer treatment, including several LHRH analogs, androgen synthesis inhibitors, and androgen receptor blockers.

The mechanism(s) by which prostate cancers become addicted to male hormones during disease pathogenesis remained enigmatic for many years after the publication of the *Cancer Research* article by Huggins and Hodges. In adult men, androgens tend to promote terminal differentiation of epithelial cells to a columnar secretory phenotype. In contrast, prostatic adenocarcinoma cells co-opt androgen receptor signaling for maintenance of a malignant phenotype. Genome and transcriptome sequencing studies appear to have delivered an explanation. The addiction may be enabled by somatic chromosomal translocations and deletions, creating fusions between androgen-regulated differentiation genes and cancer genes (9). Androgen deprivation, like that performed by Huggins and Hodges, would reduce fusion gene expression and undermine or antagonize the malignant phenotype—truly acting as a molecularly targeted therapy.

Remarkably, in the article, Huggins and Hodges also correctly speculated about sources of future treatment resistance: "the most ready explanation for variations in serum acid phosphatase following orchiectomy as well as the failure of some values to reach the normal range may be postulated by assuming varying amounts or activity of androgens produced in extragonadal sources in different individuals" (1). In current practice, although LHRH analogue reduction of circulating androgens for men with prostate cancer almost always leads to a relief of disease-related symptoms, to a diminution in blood biomarkers of disease activity (usually serum PSA), and to an improvement in radiographic images of disease sites, these benefits are all too often short-lived. Inevitably, the disease progresses to what is now termed "castration-resistant prostate cancer" (CRPC). A major mechanism by which CRPC maintains its addiction to androgen receptor signaling is by responding, as Huggins and Hodges anticipated, to the low levels of androgens produced in extragonadal sources. As a consequence, to combat CRPC, a flurry of new drug discovery and development has delivered androgen biosynthesis inhibitors, such as abiraterone, and androgen receptor antagonists, such as enzalutamide (10).

The classic 1941 Huggins and Hodges article in *Cancer Research* truly documents a timeless and remarkable translational research achievement. In revisiting the work, many of the findings seem quite modern. A molecular pathway, androgen signaling, is implicated in the malignant phenotype of a lethal disease, metastatic prostate cancer. Molecularly targeted treatment, reduction of circulating androgen levels by orchiectomy or estrogen administration, is assessed using serum biomarkers of the prostate cancer, of the androgen signaling pathway, and of metastatic prostate cancer progression. Mechanisms of treatment resistance fueling the emergence of CRPC are anticipated. The impact on human health, even 75 years later, is enormous.

Charles Huggins' humility upon receiving his Nobel Prize seems almost out of place: "A cancer worker utters the mariner's prayer: `Oh, Lord, Thy sea is so vast and my bark is so small' (11)."

Received November 17, 2015; accepted December 8, 2015; published online January 15, 2016.

References

1. Huggins C, Hodges CV. Studies on Prostatic Cancer: I. The effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.
2. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909–16.
3. Han M, Piantadosi S, Zahurak ML, Sokoll LJ, Chan DW, Epstein JI, et al.. Serum acid phosphatase level and biochemical recurrence following prostatectomy for men with clinically localized prostate cancer. Urology 2001;57:707–11.
4. Robison R. The possible significance of hexosephosphoric esters in ossification. Biochem J 1923;17:286–93.
5. Kay HD. Plasma phosphatase in osteitis deformans and in other diseases of bone. Br J Exp Pathol 1929;10:253–6.
6. Cox RL, Crawford ED. Estrogens in the treatment of prostate cancer. J Urol 1995;154:1991–8.
7. Blackard, CE, Doe RP, Mellinger GT, Byar DP. Incidence of cardiovascular disease and death in patients receiving diethystilbestrol for carcinoma of the prostate. Cancer 1970;26:249–56.
8. The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1984;311:1281–6.
9. Rubin MA, Maher CA, Chinnaiyan AM. Common gene rearrangements in prostate cancer. J Clin Oncol 2011;29:3659–68.
10. Knudsen KE, Scher HI. Starving the addiction: new opportunities for durable suppression of AR signaling in prostate cancer. Clin Cancer Res 2009;15:4792–8.
11. "Charles B. Huggins - Facts," Nobelprize.org. Nobel Media AB 2014. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1966/huggins-facts.html.

Commentary on Huggins and Hodges: "Studies on Prostatic Cancer"

William G. Nelson

Cancer Res 2016;76:186-187.