EVOLUTION AND REVOLUTION IN CANCER CARE
REFLECTIONS ON 30 YEARS OF CLINICAL RESEARCH
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DOING RESEARCH WITH IMPACT....

- Only one rule........
DOING RESEARCH WITH IMPACT….

- ASK AN IMPORTANT QUESTION!
“IMPORTANT” IS NOT THE SAME AS “INTERESTING”……

- Almost anything that is interesting might be potentially important
- Impact depends on the immediacy (actionability) of the importance
- Will it immediately change medical practice?
PROSTATE CANCER: 1986-1990

- Almost no level 1 evidence!!
- Mortality rates around 12,000 pa in UK

- Is treatment necessary for those in whom it is possible?
- Is treatment possible for those in whom it is necessary?
“Latent” prostate cancer; up to 80% of men have it by the age of 80!

A disease of the elderly (as viewed in 1990)

Outcomes after “watchful waiting”

Do we cure anyone, with M0 disease, or do we just treat those who don’t need it?
I AM THE BEST BETTER THAN THE REST

- Surgery?
- Radiotherapy?
- Monitoring?
PROSTATE CANCER AND THE JOHN WEST EFFECT

Only randomised comparisons are valid!
LOCALISED (T1-T2) PROSTATE CANCER DETECTED BY PSA
10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

...FOR THOSE IN WHOM IT IS NECESSARY....
LOCALLY ADVANCED PROSTATE CANCER 1990: NIHILISM OR OPTIMISM?

- Hormone therapy: PALLIATIVE
- Radiotherapy: CURATIVE
- MRC Survey 1995: “….these men all have occult micro-metastatic disease. Giving them radiotherapy is meddlesome and unkind....”

THE BOTTOM LINE: NON-METASTATIC DISEASE

- Treatment IS possible for some men who need it
  - Those with locally advanced disease
  - Combined radiotherapy and hormone therapy
- Treatment MAY NOT BE necessary for most men with PSA-detected localised disease
  - Active monitoring may result in more disease progression
- 15 and 20 year follow up is needed
Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, The University of Chicago, Chicago, Illinois)

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Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in carcinoma of the prostate in normal men. We shall demonstrate that the acid phosphatase of serum is reduced in metastatic carcinoma of the prostate by decreasing the activity of androgens through castration or estrogenic injections and that this enzyme is increased by injecting androgens. We have been unable to find previous observations indicating any relationship of hormones to carcinoma of the prostate gland.

An enzyme capable of hydrolyzing phosphoric esters was discovered by Green and Hunter (4) in unconverted semen and saliva. Robinson (5) found that this enzyme was particularly high in activity in growing hones and in urine and that its activity was greatest at pH 5 to 7. The "alkaline phosphatase" was found by Lee (6) to be increased in the serum in certain bone diseases including carcinoma of bone and liver, and work has shown that among these conditions is carcinoma of the prostate.

Davis (7) and Benzon and Mielke (8) discovered that there occurs in the seminal and kidney of some men, in addition to the alkaline phosphatase, a phosphatase with an activity maximum at pH 4.5. An enzyme believed to be identical with this "acid phosphatase" was found by Kamsler and Wolff (9) to be present in very large amount in the human prostate gland. This finding of great activity of acid phosphatase in the prostate gland was confirmed and extended to include prostate cancer by Gotshalk, Sirota, and Gutman (10). The serum of certain patients with disseminated prostatic carcinoma was found by Gotshalk and Gutman (11) and Ramey and Woodard (12) to exhibit increased acid phosphatase activity. Robinson, Gutman, and Gutman (13) demonstrated that the acid phosphatase activity levels of 24 patients with carcinoma of the prostate were correlated with the degree of prostatic involvement. The serum in men with carcinoma of the prostate is associated with the appearance of spread of metastasis. In patients with disseminated breast metastasis, this parallels dissemination of the primary tumor and thus is of value in prognosis.

Methods and Materials

The phosphatase activity of serum was determined by the method of King and Armstrong (14) using 1.3 mM allantoin monophosphate as substrate. The buffers used were 0.05 M barbituric acid at pH 9.5, and 0.05 M phosphate-citrate buffer at pH 7.5. All urines were treated in duplicate and were added directly to buffer-substrate solutions without dilution; they were incubated at 37°C for 30 minutes. Preliminary observations revealed that all solutions were at this temperature before testing. Blocks were run by adding the protein phosphatase to the buffer-substrate solution before adding serum. Colorimetric procedures were carried out with the Evelyn photoelectric colorimeter using a 660-mFilm. The results are expressed in King and Armstrong units, a unit being defined as that degree of phosphatase activity which at pH 9.5 (or pH 7.5, respectively) and 37°C will liberate 1 mg of phens from the specific buffer-substrate solution in one-half hour.

Phosphatase determinations at pH 5.5 and 9.5 were made on the serum of 40 normal men, of 20 men with benign prostatic hypertrophy, and of 47 men with carcinoma of the prostate. The diagnosis of carcinoma of the prostate gland was derived from one or more of the following procedures: rectal palpation, cystoscopic examination, transurethral resection with microscopic examination, or roentgenologic evidence of skeletal metastases. Necropsy was obtained in 2 cases. All patients had a 4- to 6-week history of the bony pain.

Eight patients who had carcinoma of the prostate with skeletal metastases and with moderate or great elevation of acid phosphatase of serum values above 10 units in 100 cc were selected for intensive study in the hospital. Each patient also had elevation of alkaline phosphatase in the serum. Both of these enzymes were determined on the serum 3 times weekly for many weeks. Bilateral castration was carried out in all. Four patients were injected with testosterone, 1 mg.
STAMPEDE AND THE MAMS REVOLUTION

Patients eligible for STAMPEDE

STARTING LONG-TERM HORMONES

RANDOMISATION

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STAMPEDE – FIRST OUTCOMES, 2015
Chemotherapy with docetaxel improves overall survival and failure-free survival, added to ADT in men with metastatic disease.

As yet, it does not improve survival in M0 patients, but it does delay treatment failure.
EVOLUTION OR REVOLUTION?
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• Where the technology is already being used, and the efficacy is great enough…
• Worldwide change in medical practice, enshrined in international treatment guidelines
• Usually, treatment benefits are modest, such that a randomised trial is needed
• Smaller changes in efficacy can still trigger a change in practice
• Modest benefits in advanced disease might translate into large benefits in early disease (docetaxel in M0 prostate cancer?....)
DRUGS WHICH PROLONG SURVIVAL IN ADVANCED, CASTRATE-REFRACTORY PROSTATE CANCER

- Docetaxel
- Cabazitaxel
- Abiraterone
- Enzalutamide
- Sipuleucel-T
- Alpharadin
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Prostate Cancer

Estimating the Impact of Randomised Control Trial Results on Clinical Practice: Results from a Survey and Modelling Study of Androgen Deprivation Therapy plus Radiotherapy for Locally Advanced Prostate Cancer

Annabelle Southa,*, Wendy R. Parulekarb, Matthew R. Sydesa, Bingshu E. Chenb, Mahesh K. Parmara, Noel Clarkea, Padaig Wardea, Malcolm Masone

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The Future: Stratified (Precision) Medicine

- Not every patient benefits from treatment....
- Some patients might benefit enormously....
THE STAMPEDE BIOREPOSITORY

COLLECT up to 7,000 tissue blocks (retrospective) and 2,000 blocks (prospective)

Underpin key translational questions

Pathology and tissue processing facilities