HOT SPOT

From the guest editor's desk

By Dr. C. Danjoux, MD, DMRT, FRCPC

The new academic year brought many changes to our program. One of the founding members of the RRRP, Lou Andersson was awarded the CANO-Pharmacia Award of Excellence in Clinical Practice by the Canadian Association of Nurses in Oncology (CANO) at their annual meeting. She also completed her PhD and is now teaching at the University of Western Ontario. Lou was involved in all the activities of the RRRP and will be missed. She has, however, agreed to continue as associate editor of **Hot Spot**. Macey Farhadian has replaced Lou Andersson. Over the past three years, our radiation therapist, Lori Holden, helped us organize our database, coordinated our clinical activities and the vertebroplasty project. She has accepted the position of radiation research therapist. Emily Sinclair is our new radiation therapist. Dr. May Tsao joined us and replaces Dr. Loblaw. Our editorial and financial manager, Danielle Nywening, is now the executive assistant of Dr. Maureen Trudeau, head of medical oncology at TSRCC.

Dr. Chow was successful in having the academic potential of the bone metastases clinic recognized at the TSRCC. Drs. Chow and Finkelstein are the co-directors of the first multidisciplinary bone metastases clinic in Canada. Their academic projects range from the study of bone metastases in the lab to innovative clinical studies of the effect of treatment on bone density and laser enhanced vertebroplasty. Dr. Chow is involved in developing an international consensus for bone metastases and is the principal investigator of an NCIC research study for the re-treatment of painful bone metastases by irradiation.

In this issue of **Hot Spot,** Dr. Vachon discusses boredom in terminal illness, Dr. S. Berry addresses the issue of "No CPR", and Dr. Bezjak reports on the interesting studies with radiosensitizer and whole brain irradiation for brain metastases. The historical vignette by Dr. Hayter is on the Radium Institute of Toronto.

The educational insert by Dr. Choo deals with the hormonal management of metastatic prostate cancer.

We hope that you find this issue interesting and informative.

Referral of patients to the rapid response radiotherapy clinic

The results of a previous survey by Dr. Charles Hayter indicated that 40% of patients referred to the RRRP clinics had missing information, which impacted on their care. The result of that study was published in the November 2001 issue of **Hot Spot** - **http://www.tsrcc.on.ca/RRRP.htm**

To ensure that relevant information is available when patients are seen in the RRRP clinics, we reviewed and modified the new patient referral procedure and changed the referral form. A copy of the new form is enclosed with this newsletter. The referral form will be posted on the TSRCC website - **http://www.tsrcc.on.ca** under information for referring physicians. We plan to monitor the impact of the new referral form and process and welcome your comments.

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Boredom in terminal illness

By Mary L.S. Vachon, RN, PhD

Several months ago, I received a call from a community nurse wanting to refer a single retired woman in her mid sixties who had just been told that she had just a few months to live. The woman was angry and said, "Now what am I supposed to do with my life? This is going to be so boring, I won't have the energy to do anything, but I'm not actually dying yet." I wondered what help I could be in this situation, but didn't need to worry as the woman refused the referral.

It was with great interest, therefore, that I attended a presentation by Dr. Steven Passik at the recent Sixth World Congress of Psycho-Oncology in Banff, Alberta.

Dr. Passik presented the results of a recent study on purposelessness, understimulation and boredom trying to redefine components of distress in advanced cancer (Passik, Inman, Kirsh et al., *Palliative and Supportive Care,* 2003, 1, 41-50).

He and his colleagues point out that the person with an acute life-threatening illness needs to deal with accepting the seriousness of the illness, dealing with separation from loved ones, ordering of one's affairs, and accepting the care from others necessary towards the end of life. The person with the somewhat now more common chronic life-threatening illness has the same concerns. However, these concerns are spread over a prolonged time and the person must also attempt to maintain self-esteem, occupational, social, sexual, and psychological role functions, and still attempt to live fully.

Dealing with the many aspects of the disease and its symptoms, patients may find that they are not able to engage in their normal role functions and they are left with time in which they are not cognitively or emotionally engaged. This may be boring.

"Boredom is a sign of not being actively engaged in one's life. Little joy is present, activity is decreased, and, if prolonged, can lead to depression and/or aggression (Frankl, *Man's Search for Meaning,* 1946).

Passik et al. studied a group of 60 women and 40 men with an average age of 62 years, most had at least a high school education. A factor analysis on 45 items showed that the items clustered into two major factors: overt boredom and boredom related to spirituality and meaning. Table One shows these items.

Not surprisingly, there is an overlap with depression, in that 37 of 51 (72.5%) of the bored patients were also suffering from depression, but 15 of 51 (29%) of the patients were potentially bored, but not depressed. In addition to depression, the boredom scale had meaningful correlates with self-efficacy, fatigue, and spirituality.

The authors suggest treating the underlying depression for those who are depressed and seeing whether treatment for depression alleviates boredom. Do they improve on the same or different time courses? They also suggest testing whether psychosocial interventions work differently on the depression and boredom. For the bored but not depressed, the authors suggest researching what types of counselling and activities help to alleviate this painful experience and give back life with a sense of purpose.

Passik et al. suggest that the subjective experience of boredom, when recognized in patients, can lead to interventions that help to occupy and activate patients. This may enable the clinician to penetrate the surface of the patient and open up a dialogue on issues of a deeper psychological and spiritual nature.

Mary Vachon, RN, PhD, is a psychotherapist in private practice. She can be reached at maryvachon@sympatico.ca.

Table One:

Factor I Overt boredom

- I feel bored
- I have difficulty keeping myself occupied
- I have trouble finding things to do that keep my interest
- I have long periods of time with nothing to do
- I sit around doing nothing
- I have too much time on my hands
- Time passes slowly
- I spend time doing mindless activities just to keep occupied

Factor II Boredom related to spirituality

- I feel a connection/closeness to a higher being or spiritual force
- My spiritual beliefs help me to understand and appreciate my life as it is at present
- My spiritual beliefs bring a sense of hope to my life
- I believe all things happen for a reason
- I believe healing comes from within
- I turn my health problems over to God or a spiritual force

Hot Spot Survey 2003

In a recent survey, **Hot Spot** readers indicated that they were familiar (40%) or very familiar (57%) with the newsletter, and that 44% read more than half while 45% read the whole issue of the newsletter. The majority (95%) was satisfied or very satisfied with the newsletter, its content, and the variety of articles in each issue. The insert was rated as very educational by 76%. Our readers indicated that they would like more information on the following four areas: recent advances in cancer care, pain management, symptom control, and the use of radiotherapy for pain management. We plan to cover more of those topics in the coming year. The responders were family doctors (29%), palliative care physicians (18%), oncologists (17%), and nurses (15%).

"No CPR" – Talking it over

By Scott Berry, MD, FRCPC

I was recently watching a TV show that featured two physicians discussing "No CPR" (no cardiopulmonary resuscitation) orders at their hospitals. One boasted that, at his hospital, a physician could write a "No CPR" order without discussing it with the patient. Needless to say, this physician attracted most of the host's attention, and for good reason – when it comes to "No CPR" orders, it's always worth talking it over with the patient or their substitute decision-maker.

For many of our patients dying from cancer, CPR is not appropriate. CPR was originally devised as a means of reviving patients whose hearts had stopped during a sudden catastrophic event, like a heart attack. We now live in a world where, unless there is a "No CPR" order on the chart, CPR is performed on every patient whose heart stops beating in the hospital, even if their death was expected. It is important to have a "No CPR" order on the chart so that in situations where it would clearly have no benefit, it is not performed. Does CPR have to be presented as a treatment option? NO! In fact, one of the pitfalls some physicians fall into is offering CPR even when they feel it would almost certainly have no benefit for a patient - for example, asking a patient with advanced cancer within a few days of their death whether they *want* CPR.

However, when writing a "No CPR" order, the fact that CPR doesn't have to be presented as a treatment option does not mean that the *issue* of CPR doesn't have to be discussed with patients. Sunnybrook and Women's College Health Sciences Centre has a policy addressing "No CPR" orders that highlights some of the important issues at stake here. While it recognizes there are situations where CPR doesn't have to be presented as a treatment option, "the patients' overall treatment plans and the goals of care should be discussed. It is prudent to let such patients know, at least in general terms, about the "No CPR" order and its rationale". Since we live in a world where people see CPR performed every week on TV on shows like "ER", they sometimes need to know why this would not be appropriate for them. The patient may disagree with your assessment of the situation and want to discuss why you feel it would not be appropriate (and in fact the Sunnybrook and Women's policy has a process for dealing with a situation where a patient or their substitute decision-maker disagrees with you). In many (and in my experience *most*) cases, patients will simply confirm that CPR or other "aggressive" measures are not what they want.

As I have pointed out in earlier columns – frank and sensitive discussions with your dying patients planning for their deaths can help improve the quality of their end-of-life care. "No CPR" orders should be part of these discussions. If you have patients for whom CPR would not be appropriate, start the discussion in the clinic so difficult situations in the hospital can be avoided. The bottom line is, when it comes to "No CPR" orders, it's always worth talking it over with the patient.

Historical Vignette:

The Radium Institute of Toronto

By Charles Hayter, MA, MD, FRCPC

The first radiotherapy centre in the Toronto area was the Radium Institute of Toronto, a privately-owned clinic established at 134 Bloor Street West by William H.B. Aikins (1859-1924), who was a prominent Toronto physician and radium pioneer. After visiting the Laboratoire Biologique du Radium in Paris and becoming impressed with the medical effects of radium, he bought a small supply of radium and opened the Radium Institute in 1910. This became the first clinic in Canada to specialize in the new medical treatment of radiotherapy.

Unfortunately, Aikins' casebooks and original treatment records do not appear to have survived. However, from 1910 to 1923 he published reports in medical journals on 123 patients (81 women and 42 men), and the numbering of the cases shows that by the end of 1923 he had treated over 3,200 cases referred from a wide area extending from Saskatchewan to the west to Québec to the east. By 1914, his radiotherapeutic equipment included a radium plaque (a flat applicator coated with a varnish impregnated with radium) worth about $350 and a tube containing radium salts worth about $1,200. The plaque could be placed directly on lesions on the skin, while the tube could be inserted into tumours or body cavities.

Aikins frequently gave papers and lectures on radium to the Toronto

Academy of Medicine and the Ontario and Canadian Medical Associations. In October 1916, a group of 24 North American physicians met in Philadelphia to organize the American Radium Society. It is a tribute to Aikins' reputation at the time that he was unanimously elected the first president of this society. As president of the premier North American organization for radiotherapy, Aikins was in a unique position to synthesize the body of evidence about the usefulness of radium in medicine at the time. This he did masterfully in his 1917 presentation before the society entitled, "The Value of Radium in Curing Disease, in Prolonging Life, and in Alleviating Distressing Symptoms." The three goals mentioned in his title remain the primary goals of cancer treatment today.

Review of city directories reveals that the institute survived into the 1940s. However, a stroll along the north side of Bloor Street today reveals no sign of this forgotten but important clinic.

Research Corner

By Andrea Bezjak, MD, MSc, FRCPC

Randomized trials of radiation +/- a radiosensitizer for patients with brain metastases at PMH and TSRCC

Brain metastases are an all-too-frequent and dreaded complication of many common types of cancers, particularly lung, breast, kidney, melanoma and others. Patients with solitary metastasis on MRI imaging, particularly if they have no active cancer elsewhere, may benefit from a more aggressive treatment approach including resection of accessible metastatic lesion followed by adjuvant whole brain radiation (WBRT), or consideration of stereotactic radiosurgery. However, these recommendations apply to very few patients with brain metastases. Cancer Care Ontario Practice Guideline Initiative will soon be coming out with practice guidelines on management of patients with brain metastasis. WBRT is the mainstay of treatment for most patients, except those with very poor performance status and poor overall prognosis.

To improve outcomes with WBRT, there is renewed interest in the use of radiation sensitizers. Radiation oncologists at the Princess Margaret Hospital and TSRCC have participated in a large international randomized trial of a new radiation sensitizer, Motexafin Gadolinium, administered as an IV infusion daily concurrent with WBRT in patients with brain metastases and good performance status. This multi-centre randomized study, supported by Pharmacyclics Inc., was recently published in **Journal of Clinical Oncology** (July 2003). A total of 401 patients were enrolled in multiple countries over a record period of time, this being one of the best accruing studies in brain metastases. A blinded events review committee determined the time to neurological progression. Standardized neurological assessment, neurocognitive testing, quality of life (QOL), and serial MRIs were also done. Despite very encouraging reports from Phase II studies, this randomized study failed to document an overall survival benefit or benefit in terms of time to neurological progression in patients on the gadolinium arm, in comparison to WBRT alone. Median survival was approximately five months, and median time to neurological progression was approximately nine months. However, in a subgroup of 251 patients with lung cancer, a significant separation of the curves between the control and experimental arm was observed. Benefit was seen in the gadolinium-treated patients in all of the outcomes, including time to neurological progression as scored by investigator (p= 0.025), and as scored by the blinded events review committee (p= 0.048). There was a reduction of deaths due to CNS causes (36% on MGd + WBRT arm, compared to 51.5% with RT alone, p=0.037). A trend in improved functional independence was also seen in the lung cancer patients, but no difference in overall QOL or radiological progression.

On a personal note, it was very satisfying to be able to offer this randomized study to patients with good performance status and relatively few extra-cranial sites of cancer. Although this aggressive treatment is not appropriate for many patients with brain metastases, the fast accrual rate and patient acceptance of the randomization and treatment clearly indicates that a small but definitive proportion of patients are candidates for aggressive treatment. A follow-up study currently in progress is attempting to define whether the benefits seen in the subgroup of lung cancer patients are true or spurious. The study has a virtually identical treatment design, i.e., randomization between WBRT (30 Gy in 10 fractions over two weeks) +/- Motexafin Gadolinium. Only patients with good performance status, limited extent of disease elsewhere, and brain metastases from lung cancer for which complete surgical resection is not contemplated are being accrued. Both of our radiation centres are participating.

If you have a patient you feel may be eligible, don't hesitate to contact one of the principal investigators (PIs) or clinical research associates (CRAs) responsible for the study. At PMH, the PI is Dr. Andrea Bezjak [telephone (416) 946-2132, fax (416) 946-4586]; the CRA is Carol Ann Buckley, pager 416-980-1795. At TSRCC, the PI is Dr. Yee Ung [telephone (416) 480-4951, fax (416) 217-1338], the CRA is Nancy Cohen [telephone (416) 480-6100 x 7336]. We anticipate that this study may help improve the outcomes in at least some patients with brain metastases, and offer some hope to patients and their families in this difficult condition.

Dr. Andrea Bezjak is a radiation oncologist at Princess Margaret Hospital, Toronto, and an Associate Professor at the University of Toronto.

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HOT SPOT

By Richard Choo, MD, FRCPC, FACR,
Radiation Oncologist, Toronto Sunnybrook Regional Cancer Centre

Androgen ablation for metastatic prostate cancer

- Metastatic prostate cancer is incurable by any therapeutic modality available at the present time.

- Androgen ablation is the treatment of choice for the management of metastatic prostate cancer.

- Composition of androgens in men
  1. Testosterone and its metabolites play a primary role for the growth regulation of normal and cancerous prostate.
  2. Circulating testosterone is a prohormone. Once it enters the stroma of the prostate, it is metabolized by 5 alpha-reductase to dihydrotestosterone, which is approximately 10 times more active than its parent molecule. This androgen metabolite binds to the androgen receptor of prostate epithelial cells, which promote prostate cell growth.
  3. Testicular androgen accounts for about 90-95% of circulating testosterone, while adrenal androgens account for approximately 5-10%.

- In 1941, Huggins et al demonstrated tumour regression and diminution of serum acid phosphotase after orchiectomy or estrogen administration in metastatic prostate cancer. Since then, many types of therapeutic maneuvers aiming to reduce androgenic stimulation of prostate cancer have been used.

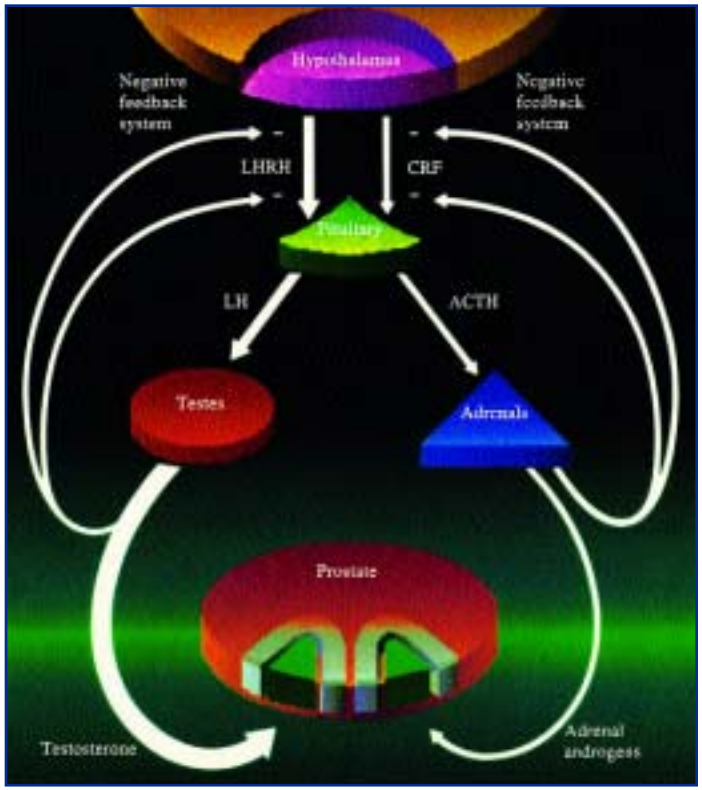
- Methods of androgen ablation and their mechanisms (Figure One - Side Two). There are two main types:
  1. Suppression of testosterone production
     a) Orchiectomy
     b) Luteinizing Hormone Releasing Hormone analog (LHRH analog): Buserelin Acetate (Suprefact), Leuprolide Acetate (Lupron), Goserelin Acetate (Zoladex)
     c) Others: Cyproterone Acetate (Androcur), Estrogen, Progesterone
  2. Antiandrogens blocking the binding of dihydrotestosterone to the androgen receptor in prostate cancer cells
     a) Bicalutamide (Casodex), Nilutamide (Anandron), Flutamide (Euflex) (*Cyproterone acetate also has antiandrogen property)
     b) Usually used in conjunction with LHRH analog or orchiectomy

- When a patient starts treatment with a LHRH analog, a 'flare' phenomenon can occur. This is due to a transient over-stimulation of receptors and a surge of testosterone secretion within the first few days of therapy. This may be associated with exacerbation of bone pain, obstruction of lower urinary tract, and neurological symptoms in a patient with spinal cord compression. This flare phenomenon can be avoided by treating the patient with an antiandrogen about one to two weeks before the initiation of LHRH analog.

- Side effects of androgen ablation
  1. Loss of potency and libido
  2. Hot flushes/Sweating
  3. Emotional lability/Mood swing
  4. Decrease in muscle mass
  5. Testicular atrophy
  6. Gynecomastia
  7. Anemia: drop of hemoglobin by 1-2 g/l
  8. Decrease in bone mineral density leading to osteoporosis

** Estrogen is rarely used nowadays, as it is associated with increased cardiovascular complications.*

- Combined androgen ablation: Orchiectomy or LHRH analog plus antiandrogen
  a) Orchiectomy or LHRH analog eliminates or suppresses testicular source of androgen. However, it does not remove androgenic stimulus from other sources of androgen such as the adrenal gland. In order to block this residual androgenic stimulus, antiandrogen is added to orchiectomy or LHRH analog. This is referred to as combined androgen ablation. It is also called 'total' or 'maximal' androgen ablation.



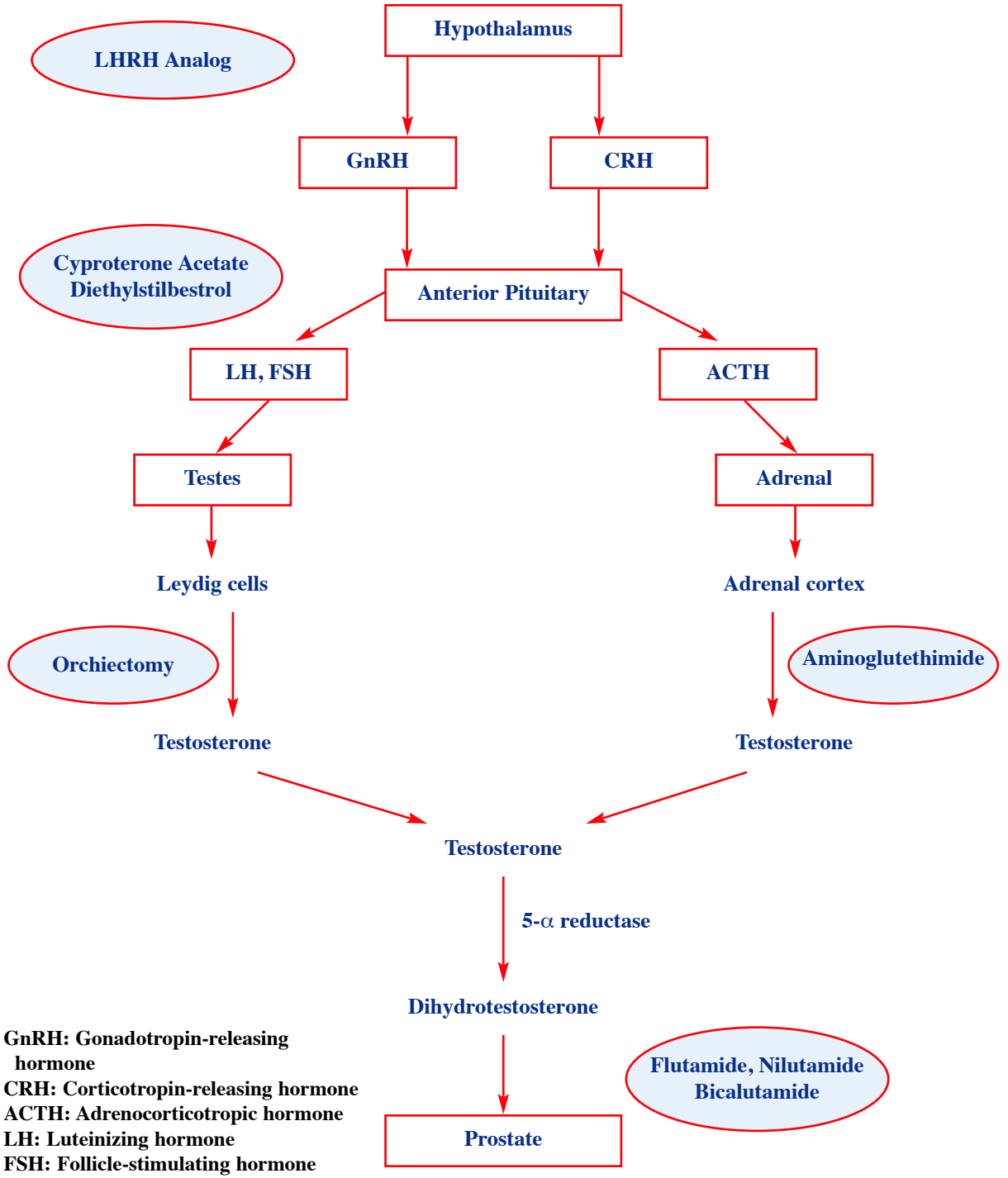
Combined androgen ablation, continued...

b) The benefit of combined androgen ablation remains the subject of widespread debate, but is considered marginal. It has more adverse effects than monotherapy using orchiectomy or LHRH analog alone. Thus its application depends on the clinical situation of the individual patient.

- Timing of androgen ablation
  a) Clinically evident distant metastasis:
  In current understanding, it is advisable to institute androgen ablation in a timely manner for patients with known distant metastasis. In one study, the initiation of androgen ablation at the time of presentation of distant metastasis reduced complications and deaths due to prostate cancer, compared to a policy of observation with androgen ablation at the time of onset of symptoms.
  b) Rising PSA after local therapy (surgery or radiation therapy) without clinically evident distant metastasis:
  Optimal timing to introduce androgen ablation for this group of patients remains uncertain. This requires further clinical studies. An individualized decision needs to be made, depending on tumour characteristics, the rate of PSA increase, and the patient's social and emotional situation.

- Androgen ablation offers major therapeutic benefits in approximately 80% of patients with metastasis. Median response duration to androgen ablation is about 18 to 24 months. Despite initial favorable response, virtually all patients develop disease progression while on androgen ablation (called 'hormone refractory' disease) and eventually die of prostate cancer. Median survival of patients with metastasis is about 24 to 36 months. The five-year survival rate is about 20 to 25%. Patients with minimal metastatic disease and good performance have better response duration and overall survival.

Figure One



GnRH: Gonadotropin-releasing hormone
CRH: Corticotropin-releasing hormone
ACTH: Adrenocorticotropic hormone
LH: Luteinizing hormone
FSH: Follicle-stimulating hormone