# CHAPTER 23
# GLUTATHIONE IN THE HUMAN MALE

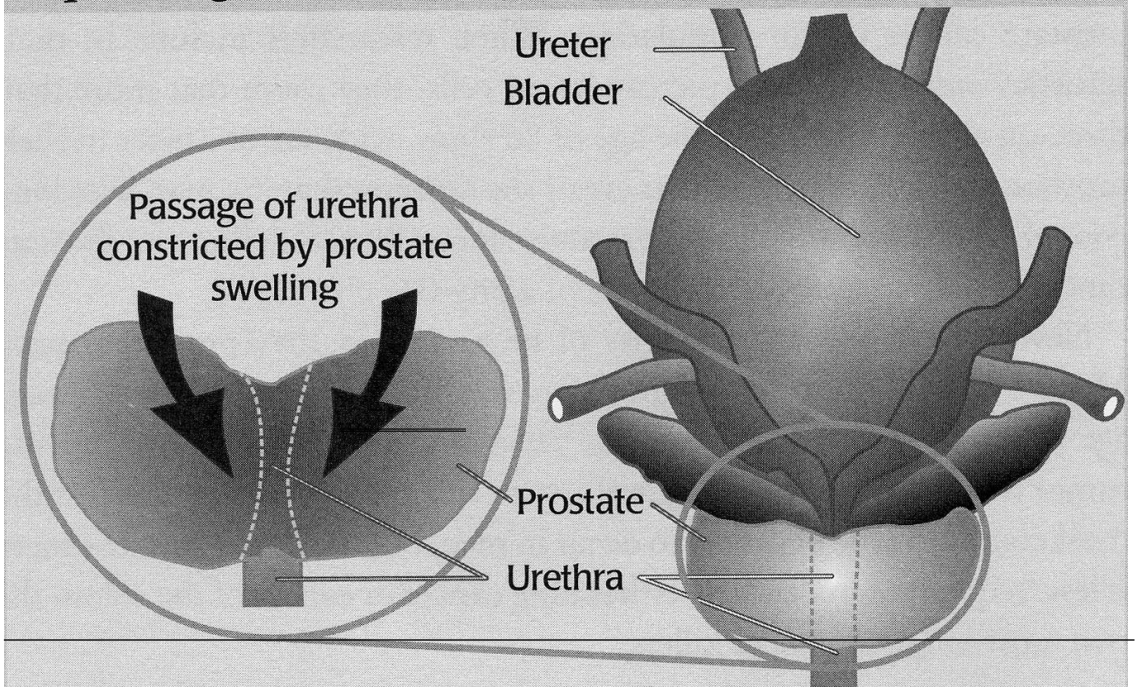
## PROSTATE PROBLEMS

Of the hundreds of animal species with a prostate gland, only humans and dogs are known to suffer from prostate cancer and prostatic hyperplasia (an overgrowth of prostate tissue). The prostate is a walnut-sized gland that surrounds the urethra, the tube that drains the bladder through the penis (see figure 41). It is responsible for the production of fluid that carries the sperm when ejaculating. Other prostate problems include infection—both acute and chronic prostatitis. The majority of men will have some sort of prostate problem in their lifetimes.

### PROSTATIC HYPERTROPHY (ENLARGED PROSTATE GLAND)

Not all prostate enlargement is cancerous. In fact most enlarged prostates are benign. Hypertrophy of the prostate is caused by an enlargement of the cells in the gland, unlike cancer, which is enlargement caused by an increase in the number of cells. This condition is age related and increases from an incidence of 8% in 30 to 40 year olds, to over 80% in men over

*Figure 41 — The urethra passes through the donut-shaped prostate gland and is easily constricted by prostate swelling*



80. Enlargement of the gland often leads to impaired flow from the bladder. Symptoms are frequent and difficult urination, a weak urinary stream, straining, dribbling, incomplete emptying and recurrent urine infections.

Traditional treatments include surgical removal of all or part of the prostate, widening of the urethral passage by such means as scraping or laser surgery, and a number of drugs that either relax the muscles at the neck of the bladder or actually shrink the prostate. Saw palmetto is an herbal therapy that is greatly valued by alternative practitioners and is now also gaining acceptance by conventional doctors as an adjunct to shrink prostate tissues.

In prostatic hypertrophy and prostate cancer the prostate overgrows for several reasons. Male hormones (androgens) have considerable influence on this growth. Physicians may prescribe anti-androgens as an antidote.

Researchers have found that abnormal growth in these tissues often corresponds to deficiencies in glutathione enzymes. One is glutathione S-transferase, which has several sub-types. The balance of these sub-types varies from normal prostate tissue to hypertrophic prostates to cancerous prostates. Several researchers propose that deficiencies in this GS H enzyme system increase the likelihood of developing both an enlarged prostate and prostate cancer.

**PROSTATE CANCER**

Well-known nutritional specialist Bonnie Liebman writes about "Death, taxes... and prostate cancer...," a poignant comment on the prevalence of prostate cancer in our population. When researchers include in their statistics individuals with pre-cancerous cells, they claim that more than three-quarters of men over the age of 8o show evidence of cancer in their prostate glands. Some scientists are of the opinion that if a man lives long enough, he will eventually get prostate cancer. By this definition, prostate cancer would certainly be a disease of aging (see chapter 6).

Nevertheless, the vast majority of men easily outlive prostate cancer. Many may not even suffer significant symptoms. Although the average age at which men are diagnosed is 72, it is usually with a slow-growing tumor that may even have begun thirty or forty years earlier. It is by far the most common type of cancer to occur in men, but death by prostate cancer is less frequent than death by either lung cancer or cancer of the colon, the two most frequent cancer killers.

Screening for prostate cancer is pursued aggressively, usually by digital rectal exam or a blood test called a PSA (prostate specific antigen). Rectal exams are a simple way to check for swelling and sensitivity. PSA levels rise in the presence of prostate cancer and are a good screening tool for this cancer. They may also indicate the effectiveness of anti-cancer treatment.

Traditional treatments include surgical removal, heat therapy, laser therapy, radiotherapy, chemotherapy, hormonal therapy and benign neglect.

Alternative therapy focuses more on slowing down the process than on curing it. Diet is important since prostatic cancer has been linked with high-fat, low-fiber diets. The use of antioxidants such as vitamin A or selenium is popular for reasons we describe below. Recently, a carotenoid called lycopene that gives certain fruits and vegetables their rich color has been linked to the prevention of prostate cancer. It seems that men who eat lycopene-rich foods (tomato sauces, dark grapes) have lower rates of prostatic disease. This theory is still under investigation.

One of the more significant series of papers to be published on glutathione and prostate cancer comes from the University of Wisconsin. Researchers there describe male hormones (androgens) as a source of oxidative stress, particularly in cancerous prostate cells. An article in the Journal of the National Cancer Institute claims that androgens stimulate free radical damage and also deplete glutathione. Given the natural decline of glutathione levels in males as they age, the article suggests that "unopposed androgen pro-oxidant stress" contributes to prostate cancer. Natural defense against oxidative stress is weakened by the decline of GSH enzymes. This is an interesting model for the development of prostate cancer.

Another finding links the loss of glutathione activity to prostate cancer. The function of a particular glutathione enzyme—glutathione-S-transferase-pi-i (GSTP1)—is almost universally lost in both cancerous and pre-cancerous prostate cells. The inactivation of this glutathione enzyme is an early event in the development of prostate cancer. Many studies have linked the loss of GSTP 1 to malignant transformation of prostatic tissues.

Medical discoveries are often a matter of chance. A very large study was undertaken by the National Cancer Institute (USA) to determine whether selenium could bring down the rate of skin cancer, notoriously caused by strong exposure to sunlight. Researchers L.C. Clarke and G.F. Combs from Cornell University and the University of Arizona already knew of selenium's

ability to raise glutathione levels (see chapter 4) and to oppose cancer-causing free radical damage from ultraviolet light. As it turned out, selenium supplementation did not affect the incidence of skin cancer, but did surprisingly and dramatically diminish the incidence of prostate cancer in the selenium supplementation group.

A more recent study from Harvard University confirms that higher selenium levels go hand-in-hand with a decreased risk of prostate cancer. It measured selenium levels in the toenail clippings of over 51,000 male health professionals between 40 and 75 years of age. Those with the highest selenium levels had the lowest chance of developing advanced prostate cancer. Note that selenium is only biologically active—and only has health benefits—when it is part of the enzyme glutathione peroxidase, through which selenium expresses its positive health benefits (see chapter 4).

Studies using whey protein isolates such as Immunocal to raise glutathione levels are underway at several research centers including McGill and Harvard Universities, where its usefulness in the treatment of prostate cancer is being weighed.

**CASE STUDY**

**Franklin was a semi-retired general practitioner who at age 68 scored a PSA reading of over 8 micrograms/liter on a routine screening exam, suggesting a high possibility of prostate cancer. In continued tests, a urologist took a cystoscopic biopsy and confirmed the diagnosis. Four out of Franklin's six biopsy sites tested positive for high-grade tumor. For personal and practical reasons, Franklin delayed aggressive treatment and opted to take 30 grams/day of Immunocal, a protein isolate that raises glutathione levels. Bimonthly PSA levels showed a gradual decline, his latest reading being 3.8 u/L. He is still being closely followed by his urologist, and his decision to undergo chemotherapy, radiotherapy or surgery will be deferred unless his PSA levels rise again.**

## MALE INFERTILITY

Many complicated factors play a part in the infertility that affects about one fifth of American couples. Ovulatory dysfunction accounts for 20%, tubal dysfunction for 30% and abnormal cervical mucus for 5%. These are all female problems. But male sperm disorders account for 35% of cases.

The problem may be low sperm count or another abnormality of the sperm, such as impaired swimming ability.

A growing body of evidence implies that oxidative stress may cause loss of sperm function. Sperm generate an excess amount of oxyradicals and these reactive oxygen molecules may lead to lipid peroxidation (oxidation of fatty substances) in the cell wall of the sperm itself. This leads to poor movement characteristics of the sperm and their impaired ability to fuse with the female's ova or egg. This understanding has opened doors for the development of innovative techniques in the treatment of male infertility.

Patients with idiopathic male infertility were compared to fertile volunteers by measuring oxidative stress, antioxidant activity and glutathione levels. Urologist I. Alkan and his team found significant differences among all parameters of both groups, suggesting that oxidation may cause infertility. Similar studies conducted by F.R. Ochsendorf at the Center of Dermatology and Andrology in Germany support these findings.

A group of reproductive biology scientists led by D.S. Irvine in Edinburgh, Scotland, is raising GSH contents in male infertility patients. In a paper entitled `Glutathione for male infertility,' he showed that GSH seems to act at the epididymis and during sperm formation as well as improving the function of ejaculated spermatozoa. Another German team headed by T. Oeda experimented with NAC (N-acetylcysteine) and showed that it reduced oxidative stress and improved impaired sperm function.

A. Lenzi's team at the University Laboratory of Seminology and Reproduction in Rome has published many papers on the use of injectable GSH in a variety of infertile males. These studies were human double-blind, cross-over studies and the therapy had consistently positive effects on sperm motility, morphology (structure), and semen quality.

### BALDING & HAIR LOSS

Human hair varies widely in texture, color, thickness and distribution. It is a sensitive tissue, prone to loss or balding (alopecia). Alopecia universalis is a rare condition of total body hair loss. Alopecia areata is loss of hair in patches. Toxic alopecia is a common cause of hair loss, usually temporary and following serious illness, fever, pregnancy, various drugs (especially those used in chemotherapy) or overdoses of vitamin A. The most common cause of hair loss is androgenic alopecia or male-pattern baldness, which varies in pattern and severity.

Normal hair grows in cycles. Anagen is the active growing phase, catagen is a brief phase when growth slows down, and telogen is a resting dormant phase, where hair falls out, hopefully to be replaced in the next anagen phase. Research shows a positive correlation between GSH content and the percentage of anagen hairs present in a scalp sample, concluding that glutathione helps maintain the hair growth cycle. Researchers theorize that free radical formation plays a role in male pattern baldness. It is possible to measure the breakdown products of oxidative stress in bald and hairy areas of the scalp. The values are doubled in the balding areas. And correspondingly, hairy areas have almost three times as much glutathione.

In male-pattern baldness, androgens (male hormones) target hair follicles, which convert them into even stronger hormones. The unfortunate result is that hair growth slows or stops. M.E. Sawaya at the University of Miami showed that the conversion of these hormones can be influenced by glutathione, suggesting that GSH plays a protective role.

Age-related GSH losses in human hair follicles is part of the total body glutathione depletion described in chapter 6 on aging. Working at the L'Oreal research lab, M. Kermici measured follicular GSH activity in men and women ranging in age from 19 to 102 years and found a significant decline up until about age seventy, then a slower second decline.

For many patients one of the more distressing side effects of cancer chemotherapy is hair loss. Rapidly growing cells such as hair cells and intestinal lining cells are the most sensitive to chemo-toxins, which quickly lead to temporary hair loss, and also cause diarrhea and cramps. Elevated GSH levels help protect these cells from chemotherapeutic agents and diminish their unfortunate side-effects.

The GSH precursor NAC enhances the tumor-killing effect of the drug doxorubicin on skin cancer in the lab, but also completely prevents the hair loss that normally accompanies this treatment. Other researchers have produced similar hair protective effects using NAC in cyclophosphamide and cytarabine chemotherapy.

## CONCLUSION

Oxidative damage and low glutathione levels has been implicated in the onset and development of many prostate problems, including cancer. GSH supplementation may provide protection against carcinogenesis in this

gland, or at least slow the development of the disease. Male infertility is associated with increased oxidative stress and low GSH levels. Elevated GSH levels may enhance the quality of sperm and increase fertility. And GSH also feeds hair follicles and may prevent or delay hair loss especially that suffered as a side-effect of chemotherapy.

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