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The Aging Male

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B. Lunenfeld

THE AGING MALE

"Old age is the most unexpected of all the things that happen to a man" (Leon Trotsky in his Diary in Exile in 1935)

The past century has witnessed a transition from a high mortality/high fertility pattern to one of low mortality/low fertility. This change of pattern resulted in a rapidly aging world population [1]. Due to the worldwide prolongation of the mean life expectancy and the drastic reduction of fertility rate it is projected that the elderly (above 65) will increase within the next 25 years by 82 %, whereas the new born only by 3 %. The working age population will increase by only 46 %. The UN project (in their 1998 revision) that by 2050, the proportion of persons above 60 will exceed for the first time the proportion of children below 15, and 13 countries will have more than 10 % of the oldest, > 80 years old, in their population. Italy will be leading with 14 %. It is expected that by the year 2050 nearly 25 % of the population of Europe will be above 65 [2]. The significant increase of the mean worldwide life expectancy at birth is a victory of human will, endurance and technology [3]. The extension of the life span made most women live nearly a third of their life span with ovarian insufficiency, and many men experience similar phenomena due to secondary partial endocrine deficiencies. The rapidity with which the world-wide population is ageing will require a sharp focus on gender issues, if meaningful policies are to be developed [4]. The promotion of healthy aging and the prevention, or drastic reduction of morbidity and disability of the elderly must assume a central role in the formulation of the health and social policies of many, if not all, countries in the next century. It must emphasize an all encompassing life long approach to the aging process beginning with preconceptual events and focus on appropriate interventions at all stages of life. Since the determinants of „aging" and of „life expectancy" extend from genetic and molecular determinants to the increasingly powerful forces of environmental, economical, technological and cultural globalization, specific measures should include the promotion of a safe environment, healthy lifestyle including proper nutrition, appropriate exercise, avoidance of smoking, drug and alcohol abuses, social interactions to maintain good mental health, and medical health care including the control of chronic illnesses. If done effectively, it should result in a significant reduction of the health and social costs, reduce pain and suffering, increase the quality of life of the elderly and enable them to remain productive and contribute to the well-being of society.

MEN, AGING AND HEALTH

In contrast to the recent and much needed attention to the social position and health status in women, men health concerns have been relatively neglected. Men continue to have a higher morbidity and higher mortality rate and life expectancy for men is significant shorter then that for women in most regions of the world [3]. The course of disease, response to disease and societal response to illness exhibit gender differences and often result in different treatments and different access to health care.

The major causes of morbidity and mortality all take effect over extended periods. Therefore, primary prevention strategies will be most effective when initiated at the earliest opportunity. Ischemic heart disease, hypertension and stroke (carotid artery intima-media thickness may be a good non-invasive method of vascular assessment) as well as lung cancer are diseases, to which primary prevention needs to be addressed. When problems are more prevalent at older ages, as with prostate and colorectal cancers and osteoporosis early diagnostic tests, such as appropriate and periodic use of laboratory tests (eg, PSA) and screening procedures can play an important role in secondary prevention and self care strategies [5]. Significant numbers of male related health problems such as changes in body constitution, fat distribution, muscle weakness, urinary incontinence, loss of cognitive functioning, reduction in well-being, depression, as well as sexual dysfunction, could be detected and treated in their early stage if both physicians and public awareness of these problems were more pervasive. This could effectively decrease morbidity, frailty and dependency, increase quality of life and reduce health service costs.

Partial Endocrine deficiency in Men (PEDAM)

The most important and drastic gender differences in aging are related to the reproductive organs. In distinction to the course of reproductive aging in women, with the rapid decline in sex hormones expressed by the cessation of menses, men experience a slow and continuous decline of a large number of hormones, but do not show an irreversible arrest of reproductive capacity in old age [6].

In the aging male, endocrine changes and decline in endocrine function involves:

1) reduced secretory output from peripheral glands due to sclerosis of blood vessels (in the interstitial tissue of Leydig cells, this process contributes for example to a large extend, to the decrease of gonadal androgens),

2) alterations in the central mechanism controlling the temporal organization of hormonal release. The heterogeneity in basal neuro-endocrine function in aging reported in the literature, is compounded by the fact that basal hormone levels are far from constant but fluctuate considerable, due to the interaction of circadian rhythmicity, sleep, and for some of the hormones intermittent pulsatile releases at different intervals. During aging a number of morphological and neuro-chemical alterations have been found in the suprachiasmatic nuclei (the central circadianpace-maker), and are likely to be responsible for the dampened circadian hormonal and non-hormonal rhythms. These are in part responsible of the age dependent decrease of the peripheral levels of testosterone, dehydroepiandrosterone (DHEA), growth hormone (GH), IGF1, and melatonin. In addition, sex hormone binding globulin's (SHBG) increase with age resulting in further lowering the concentrations of free biologically active androgens. Since however some Leydig cell function persists during aging, *stricu sensu* the andropause does not exist.

However a growing body of literature supports the view point that a true decrease in gonadal and adrenal bio-available androgens [7, 8] as well as of GH [9] develops in most aging men and these result in "partial endocrine deficiencies". The partial endocrine deficiency syndrome of the aging male (PEDAM) may be associated with a broad spectrum of symptoms (see table 1).

Moreover, in aging men also melatonin secretion decreases, and the circadian periodicity of melatonin is gradually disrupted. Sleep in these older men is shallow and fragmented [10]. These alterations influence particular growth hormone secretion, which occurs with deeper stages of sleep (SW = Slow wave sleep) In men, approx. 70 % of the daily GH output occurs during early sleep (SW). During aging, SW sleep and GH secretion decrease with the same chronology, raising the possibility that the peripheral effects of the hyposomatotropism of the elderly may partially reflect age-related alterations in sleep-wake homeostasis. While the association between sleep and GH release has been well documented, there is also evidence indicating that components of the somatotropic axis are involved in regulating sleep [11]. It has been shown that in elderly men the decrease in melatonin secretion and the circadian periodicity of melatonin was correlated with a number of disorders (see table 2).

The secretion of GH from the anterior pituitary and it's tissue mediator IGF-I declines with increasing age (somatopause). This observation, together with the changes in body composition associated with organic GH deficiency in adults, has led to the suggestion that the elderly without hypothalamic-pituitary disease are GH deficient and may

Table 1: Symptoms of partial endocrine deficiencies in aging men

1. A decrease of general well-being
2. A decrease of sexual pilosity
3. A decrease of libido
4. A decrease of cognitive function
5. A decrease of red blood cell volume
6. A decrease in muscle strength
7. Osteoporosis
8. A decrease of immune-competence
9. An increase of fat mass and change in fat contribution and localization
10. An increase in cardio-vascular events

Table 2: Disorders correlated with decrease in melatonin

1. Increase of sleep disorders
2. mood disorders
3. decay in cognitive functions
4. regulation of platelet production

benefit from GH therapy. However it must be stressed that the impact of organic disease of the hypothalamic-pituitary axis in the elderly may result in a further reduction in GH secretion of up to 90 %. This reduction in GH secretion is sufficient to cause a fall in the serum insulin-like growth factor-1 (IGF-1) concentration, abnormal body composition and abnormal bone turnover, although bone mineral density is unaffected [12]. Older men are more sensitive to infections, sepsis, and cope more difficult with sepsis. They respond poorly to healing and to repair of bone fractures. The administration of growth hormone can attenuate the catabolic response to injury, surgery, and sepsis.

Hormone Replacement Therapy in the aging male (HRT)

In cases of endocrine deficiencies, traditional endocrinology aims to replace the missing hormone or hormones with substitutes. It has been demonstrated that interventions, such as hormone replacement therapies and use of anti-oxidant drugs may favorably influence some of the pathological conditions in aging men, by preventing the preventable and delaying the inevitable (Lunenfeld, 1999).

A comprehensive medical, psycho-social and life-style history, a physical examination and laboratory testing is essential for the diagnosis and management of PEDAM. Acute, chronic or intercurrent diseases must be taken into consideration prior to initiating any hormonal substitution therapy. Hormone substitution should only be performed by physicians with basic knowledge and clinical experience in diagnosis, treatment and monitoring of endocrine deficiencies.

In the era of evidence-based medicine, we have however to acknowledge that data on hormone replacement therapy in the aging male, is mostly circumstantial, based on experience in treatment of transitional hypogonadism in young men or in chronic hypogonadism due to disease or experiments of nature. However over the past several years, there has been an increasing interest in evaluating whether testosterone therapy (male HRT) might be beneficial for certain older men in preventing or delaying some aspects of ageing, and a number of *prospective studies on hormone replacement therapy in the aging male were performed.*

Peter Marin (1992) [13] performed a randomized, placebo-controlled study of 8 month duration with testosterone undecanoate (TU) 160 mg/day in healthy, obese (BMI > 25 kg/m^2), middle-aged (> 45 yrs) men. Their mean plasma testosterone was 16 nmol/L (range 9–21 nmol/L). Body composition was measured by CT-scan. Within 8 month sagittal abdominal diameter decreased from 27.0 to 24.6 cm ($p < 0.01$), whereas with placebo no change was observed. He also reported: improved general well-being ($p < 0.05$), feeling of improved energy ($p < 0.1$), cardiovascular safety aspects such as increased insulin sensitivity after glucose load ($p < 0.01$), as well as reduced fasting glucose levels ($p < 0.05$).

Morley (1993) [14] reported that males who received testosterone had a significant increase in testosterone and bioavailable testosterone concentration, hematocrit, right hand muscle strength and osteocalcin concentration. They had a decrease in cholesterol (without a change in HDL-cholesterol) levels and decreased BUN/creatinine ratios. These results were confirmed by Snyder et al. [15] who concluded that increasing the serum testosterone concentrations of normal men over 65 yrs of age to the mid-normal range of young men decreased fat mass, principally in the arms and legs, and increased lean mass, principally in the trunk. Snyder et al also showed that increasing the serum testosterone concentrations of normal men over 65 yrs of age to the mid-normal range for young men did not increase lumbar spine bone density overall, but did increase it in those men with low pretreatment serum testosterone concentrations (< 7 nmol/l). The prospective studies of Arver et al [16], Lisa Tenover [17, 18], and Bebb [19] performed on elderly men with verified testosterone deficiency confirmed earlier work and indicated that androgen replacement: increases bone density, joy of life and aggression in business, improvement of physical & psychic well-being, libido, a decrease of fat mass, a change in fat contribution and localization as well as a decrease in cardio-vascular events.

The decision to start hormone replacement therapy in men

should only be taken after obtaining objective evidence of hormone deficiencies, after exclusion of secondary causes of endocrine dysfunction and after making the balance of risks and expected benefits of the replacement therapy. Prior to initiation of testosterone therapy all patients should have a digital rectal examination and a serum prostate specific antigen (PSA) level measured, this should be less then 3 ng/ml and should be repeated within 3 month following initiation of therapy.

Replacement therapies for secondary DHEA deficiency are being developed. A 100 mg daily dose of DHEA for 6 month restored serum DHEA levels to those of young adults and serum DHEA sulfate (DS) to levels at or slightly above the young adult range [20]. Serum cortisol levels were unaltered, consequently the DS/cortisol ratio was increased to pubertal (10 : 1) levels. In relation to baseline, DHEA administration resulted also in an elevation of serum IGF-I levels in men (16 ± 6 %, P = 0.04). Serum levels of IGFBP-1 and IGFBP-3 were unaltered, fat body mass decreased 1.0 ± 0.4 kg (6.1 ± 2.6%, P =0.02) and knee muscle strength 15.0 ± 3.3 % (P = 0.02) as well as lumbar back strength 13.9 ± 5.4 % (P = 0.01) increased.

Replacement therapy protocols for GH and melatonin deficiencies are currently under development. Within the next few years standardized indications, effective products and treatment protocols will become available.

Administration of growth hormone (GH) induces increases in both bone and lean body mass and a decrease in fatty tissue in elderly men with GH deficiency [21–23]. The dose of GH required to maintain serum IGF-I levels in the normal range while minimizing side-effects in this group of patients however, has not been fully assessed. Toogood [24] demonstrated that the GH replacement dose in elderly subjects is considerably lower than that required by younger adults with GH deficiency. According to Janssen et al [25] GH therapy at doses of 0.6 and 1.2 IU/day in male and female patients, respectively, is, in general, able to increase serum IGF-I into the normal range after 12 weeks of treatment, without reaching supranormal levels of serum IGF-I. This dose could, therefore, be a starting dose in GH-deficient elderly patients. None of the low dose GH treated patients exhibited a supernormal IGF-I level [24].

Hormone replacement therapy alone will not suffice to increase muscle strength, decrease fat mass and change in fat contribution and localization in aging men. Proper nutrition and physical exercise targeted at specific muscle groups is mandatory in order to obtain satisfactory results. Moreover some authors suggest that resistance exercise training improved muscle strength and anabolism in older men, and these improvements were not enhanced when exercise was combined with daily GH administration [26].

Conclusion

When data of long-term well-controlled studies will have become available, long-term substitution therapy with one or more hormonal preparations will most probably – if used correctly – improve the quality of life of aging men and delay many of the symptoms of the aging process. Although it is probably not unrealistic that in the future HRT in men will become as common as in women today, but it goes without saying even today there is strong evidence that a healthy lifestyle with regular physical and mental activity has significant physiological, psychological and social benefits for older persons. It is my sincere hope that the next few years will enrich us with facts and clarify the state of our present knowledge, permitting us to recognize some of the missing links and give us the tools and methodology to design and plan ways to understand aging of men, permit us to help to improve the quality of life, prevent the preventable, and postpone and decrease the pain and suffering of the inevitable. In light of this, public awareness of medical knowledge needs to be increased and basic, clinical, socio-economic and epidemiological research intensified. This will necessitate a quantum leap in multi-disciplinary and internationally coordinated research efforts. Such efforts should be supported by the establishment of new partners between inter-governmental, governmental, commercial and voluntary sectors.

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Prof. Dr. med. Bruno Lunenfeld

Bruno Lunenfeld was born in Vienna (Austria) in 1927, received his scholastic education in Austria, United Kingdom, and Israel. He graduated from the Medical School in Geneva, Switzerland. Following his post-graduate work in Geneva he returned to Israel and joined the Weizman Institute as senior scientist till 1969, and then headed the Institute of Endocrinology at the Sheba Medical Center from 1969–1992. He was also a Consultant and member of Expert Committees at the World Health Organization from 1967 to 1992. From 1967–1995 he was Professor of Endocrinology at the Faculty of Natural Sciences and Mathematics, Department of Life Sciences, Bar-Ilan University. Since 1995 he is Professsor Emeritus at the Faculty of Life Sciences, Bar-Ilan University, Medical Director, International Fertility Institute, Ra'anana, Israel, President of the International Society for the Study of the Aging Male (ISSAM), and editor of the Journal „The Aging Male".

Professor Lunenfeld was the first to study and assess the combination of testosterone and estrogens in the menopausal syndrome, and this was also his medical thesis in 1954. He is best known for his pioneering work in human reproduction. Especially for extraction, purification and introduction of human menopausal gonadotropins (hMG) for clinical use (1953–1961) in unovulatory women and hypopituitary-hypogonadotropic men. He was instrumental in the creation of an international standard for gonadotropins, the classification of infertile patients and of the hyperstimulation syndrome. He has made significant contributions to the understanding of follicular recruitment, rescue, selection, growth and development, the ovulatory cycle and the mechanism of action of gonadotropins in ovaries and testis. Professor Lunenfeld pioneered the use of GnRH analogues as stimulators and inhibitors of the gonads and as a result the effect on cells, tissues, organs or tumors depending on gonadal activity. He chaired five international symposia of GnRH analogues in cancer and reproduction and will preside the 6th International Symposia which will take place in Geneva 8–11 February 2001.

He was instrumental in the study of the aging male, was the founder and first president of the International Society for the study of the aging male, and editor of the Journal "The Aging Male". He organized (in collaboration with the World Health Organization) and chaired the first world and second congress of the Aging Male in Geneva, February 1998, and 9-13 Feb. 2000. He will also preside the 3rd World Congress of the Aging Male which will take place in Berlin, February 2002.

Professor Lunenfeld is a member of the British, Swiss and American Endocrine Societies. He holds honorary memberships in the German and Italian and French Society of Gynecology and Obstetrics, the German Endocrine Society, the Austrian Society of Fertility and Sterility and the Brazilian Society of Human Reproduction. He was nominated Fellow (ad eundem) of the Royal College of Obstetrics and Gynecologists (UK) in 1981 and became an Honorary Fellow of the American College of Obstetricians and Gynecologists in 1991. In 1995 he became honorary member of the European Society of Human Reproduction and Embryology (ESHRE) and the International Federation of Fertility Societies (IFFS).

For his scientific achievements he received the "Pliskin Prize" from the Israel Trade Union Sick Fund in 1962; the "Yofe Prize" from the Ministry of Health in 1963, the „Michaelis Raute" medal in Kiel, Germany in 1979 and the Jacob Henley Medal of the University of Goettingen in 1992. In 1983 he received the special recognition award of the United States Public Health Service in recognition of his outstanding contribution in the promotion of health. In 1995 he received the "Verdienstkreuz 1. Klasse" (German Government "Order of Distinction") signed by the President of Germany, Roman Herzog.

Professor Lunenfeld's publications number more than 370. He has furthermore published 19 books and edited 5, in various languages. He gave more than 700 invited lectures and chaired or co-chaired more than 100 sessions at national/international meetings. He trained more than 200 local and foreign physicians and supervised more than 50 MD, MSC, and Ph.D. students.

Professor Lunenfeld's Curriculum Vitae appears since 1979 in "Who's Who in the World of Medicine", in the 16th edition of the "Dictionary of International Biography" and in the 8th edition of Asia's Who's Who of men and women of achievement.

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