The role of oestrogen in the pathogenesis of obesity, type 2 diabetes, breast cancer and prostate disease

Graeme P. Williams

A detailed review of the literature was performed in a bid to identify the presence of a common link between specific hormone interactions and the increasing prevalence of global disease. The synergistic action of unopposed oestrogen and leptin, compounded by increasing insulin, cortisol and xeno-oestrogen exposure directly initiate, promote and exacerbate obesity, type 2 diabetes, uterine overgrowth, prostatic enlargement, prostate cancer and breast cancer. Furthermore these hormones significantly contribute to the incidence and intensity of anxiety and depression, Alzheimer's disease, heart disease and stroke. This review, in collaboration with hundreds of evidence-based clinical researchers, correlates the significant interactions these hormones exert upon the upregulation of p450 aromatase, oestrogen, leptin and insulin receptor function; the normal status quo of their binding globulins; and how adduct formation alters DNA sequencing to ultimately produce an array of metabolic conditions ranging from menopausal symptoms and obesity to Alzheimer's disease and breast and prostate cancer. It reveals the way that poor diet, increased stress, unopposed endogenous oestrogens, exogenous oestrogens, pesticides, xeno-oestrogens and leptin are associated with increased aromatase activity, and how its products, increased endogenous oestrogen and lowered testosterone, are associated with obesity, type 2 diabetes, Alzheimer's disease and oestrogenic disease. This controversial break-through represents a paradigm shift in medical thinking, which can prevent the raging pandemic of diabetes, obesity and cancer currently sweeping the world, and as such, it will reshape health initiatives, reduce suffering, prevent waste of government expenditure and effectively transform preventative medicine and global health care for decades. *European Journal of Cancer Prevention* **19:256–271 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Considering that the incidence of obesity, type 2 diabetes, dementia, prostate cancer and breast cancer is now reaching pandemic levels in westernized economies, a detailed review of the literature was carried out in a bid to identify a common link between hormone interactions and the pathogenesis of these prevalent diseases.

In the USA, Canada, Australia and Britain the incidence of obesity is more than 24%, and their combined obesity/overweight incidence rate has exceeded 60% (World Health Organization, 2004–2006), such that obesity and type 2 diabetes are currently causing more deaths than any recent war or flu epidemic.

By 2025, 380 million people, one in 14, are expected to suffer from type 2 diabetes, the world's fastest growing chronic disease (International Diabetes Foundation, 2007).

Anxiety, depression, hypertension, heart disease, cardiovascular disease, cerebral vascular disease and stress-related illnesses are growing at a higher rate than most economies.

About 80% of women and men suffer from benign uterine and prostate conditions; and breast cancer and prostate cancer, respectively, are now the most common cancers in the world their rates increasing by 31% in each decade.

This detailed analysis reveals an overwhelming plethora of evidence, as to how oestrogen, leptin, insulin, xeno-oestrogens and stress hormones interact to directly and indirectly cause our '21st century pandemic' and its insidious progression from normal function to symptomatic illness, to established disease, and ultimately, to premature death.

Hormone interaction

Normal hormone function

Oestrogen

Essential for normal fertility, it stimulates endometrial and myometrial growth, increases subcutaneous fat distribution, increases neuromuscular action potentials and muscle excitability, increases ductal breast growth, produces secondary sexual characteristics and increases salt and water retention (Ganong and Lange, 2005).

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Oestrogen is normally produced by ovarian follicles, adipose cells and breast tissue in women, and by adipose cells and prostate tissue in men.

Leptin

This adipocytokine, a peptide released by adipose cells, is often considered a satiety hormone in excess to restrict eating by reducing neuropeptide Y action on the paraventricular nucleus of the hypothalamus. It probably acts more as an appetite stimulant in humans under conditions of leptin deficiency or leptin nonrecognition, to increase neuropeptide Y release and to stimulate eating.

Insulin

In normality, the consumption of high glycaemic-product carbohydrates, produce increased insulin secretion and sensitivity necessary to convert glucose to glucagon, increase fatty acid oxidation, reduce lipid accumulation in muscle and to assist the entry of glucose into cells.

Stress hormones

The adrenal secretion of corticosteroids, glucocorticoids, cortisol and adrenaline in the short-term normal stress response increases glucose availability to drive the 'fight or flight' mechanism by increasing gluconeogenesis and increasing hepatic glycogenolysis; with protracted action, they increase mobilization of amino acids from skin, bone and muscle and increase visceral adiposity.

Progesterone

Principally produced by the corpus luteum in sufficient quantity at normal ovulation to adequately oppose the growth and irritant properties of endogenous oestrogen. It also inhibits the action of p450 aromatase, the enzyme which catalyses the aromatization of testosterone (and androstenedione, ASD) into endogenous oestradiol (and oestrone) in adipose, breast and prostate tissue. In early reproductive life, late reproductive life and under times of stress, there is often insufficient progesterone production at ovulation to adequately oppose the normal oestrogen present.

During 'ovulopause', the absence of ovulation (whether it be caused by follicle exhaustion, severe stress, contraceptive pill use, the absence of ovaries or being male), no progesterone is produced to offset the normal endogenous production of oestrogen, and so the physiological growth and irritant effects of unopposed oestrogen become evident – the so-called 'symptoms of menopause and andropause'.

The symptomatic progression

Although the rate and degree of metabolic change varies among individuals as a consequence of their in-utero and in-vivo hormone exposures, their genetic backgrounds, predispositions, physical activity and dietary habits, the process toward symptomatic progression, in general, follows the same path – the cyclic upregulation of p450 aromatase to produce more intracellular oestradiol.

Any compound that upregulates aromatase will increase unopposed intracellular bioactive oestradiol concentrations, and as such will increase the incidence of oestrogen-mediated growth disorders.

The process in brief

The presence of an increasing concentration of unopposed endogenous oestradiol (whether it be associated with the reduced progesterone production of impaired ovulation or by the gradual increase in adipose cell production of oestradiol in men and women) upregulates the production of 11β-hydroxysteroid dehydrogenase 10-fold (Dieudonne *et al.*, 2006), (the enzyme that catalyses the conversion of inactive cortisone to active cortisol), which increases intracellular cortisol, and in turn, upregulates aromatase another 9-fold (Thorton *et al.*, 2006).

Although daily stress increases circulating cortisol to accentuate aromatase upregulation, its action in stimulating the increased consumption of palatable carbohydrates (Dallman *et al.*, 2007) is far more significant as it provokes an insulin response which upregulates aromatase a further 6-fold (Samad, 2007).

With further stress and continued eating, the upregulated aromatase creates even more oestradiol, to further upregulate 11β-hydroxysteroid dehydrogenase, which cyclically amplifies the production of more cortisol and further oestradiol to stimulate oestrogen receptors and accentuate growth in oestrogen-sensitive, aromatase-active tissues – fat, breasts, womb and prostate.

The process in detail

Adipocyte-derived leptin and oestradiol both upregulate 11β-hydroxysteroid dehydrogenase (Dieudonne *et al.*, 2006; Paulsen *et al.*, 2007), the enzyme that converts inactive cortisone to bioactive cortisol, to increase the size and number of adipocytes and to increase both intracellular and circulating cortisol. In turn, the cortisol upregulates adipocyte p450 aromatase 9-fold (Thorton *et al.*, 2006), the product of which further upregulates itself (Kinoshita and Chen, 2003) and positively feeds back to cyclically upregulate 11β-hydroxysteroid dehydrogenase 10-fold (Dieudonne *et al.*, 2006), and to stimulate increased leptin production.

The oestrogen (Santner *et al.*, 1997; Dieudonne *et al.*, 2006) and leptin (Daghestani *et al.*, 2007; Geisler *et al.*, 2007), both upregulate p450 aromatase to further increase extra-glandular oestrone and oestradiol production (Catalano *et al.*, 2003; Dundar *et al.*, 2005; Dieudonne *et al.*, 2006) from ASD and testosterone, and potentiate the action of oestradiol on oestrogen receptor-α (ER-α)

(Catalano *et al.*, 2004; Sulkowska *et al.*, 2006; Cirillo *et al.*, 2008) to stimulate breast tissue growth and to further increase subcutaneous fat deposition (Shin *et al.*, 2007) (Fig. 1).

The physical effects of illness and the psychological stress associated with the concern of being loved and accepted by family and peers, compounded by work pressure, financial stress and the perceived urgency of daily living, all contribute to an ever-increasing burden of stressors in the community.

Chronic stress increases palatable food intake (Dallman *et al.*, 2007), including foods that contain 30% sucrose (like many breakfast cereals, cakes, biscuits and confectionary), which increases the output of hypothalamic corticotropin releasing hormone (Foster *et al.*, 2009), pituitary adrenocorticotrophic hormone and adrenal corticosterone to promote further palatable eating and to provoke a normal insulin response, which in turn, increases leptin output (Thomas *et al.*, 2000; Falconnier *et al.*, 2003; Manderson *et al.*, 2003; Lindsay *et al.*, 2004), and upregulates aromatase (Samad, 2007) and oestrogen receptors (Oestrogen Receptors, 1998) to increase subcutaneous fat deposition (Shin *et al.*, 2007), and reduce lipolysis (Pedersen *et al.*, 2004). In effect, this builds the total fat mass to further increase leptin (Castracane *et al.*, 1998) and adipocyte oestrogen output (Vona Davis *et al.*, 2007), which initiates the process of impaired leptin receptor signalling (Kellerer *et al.*, 2001; Strat *et al.*, 2005; Garofolo *et al.*, 2006; Ishida-Takahashi *et al.*, 2006).

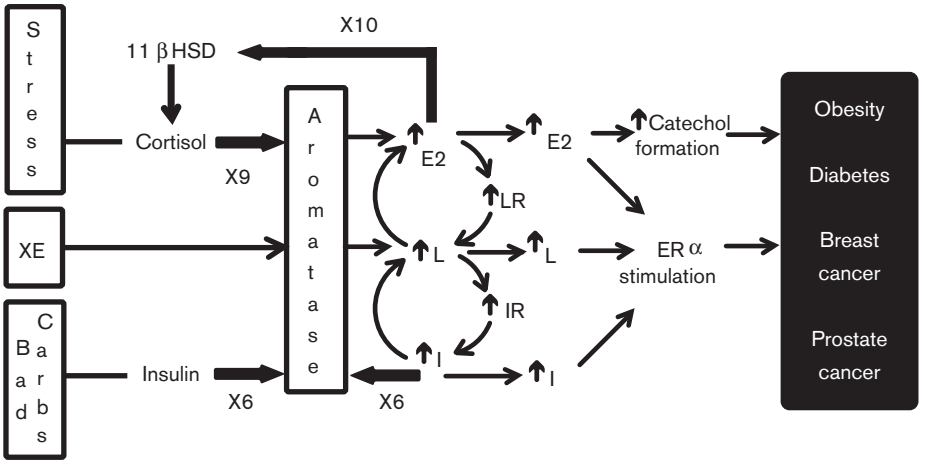
As obesity increases in men and women, there is overexpression and increased activation of 11β-hydroxysteroid dehydrogenase (Paulsen *et al.*, 2007) within local adipose tissue [independent of plasma cortisol levels (Espindola-Antunes and Kater, 2007)], which accentuates intracellular cortisol production and further upregulation of aromatase. In turn, circulating cortisol levels increase, which affects the development of dysmorphic features, central obesity, raised blood pressure, insulin resistance and dyslipidaemia.

The rising intracellular oestrogen concentration stimulates increased leptin production by fat cells (Tanaka *et al.*, 2001), increases adipogenesis by ER-α stimulation and altered Janus kinase (JAK) interactions (Iguchi *et al.*, 2008) and inhibits leptin receptor expression (Ishida-Takahashi *et al.*, 2006; Revillion *et al.*, 2006) by altering downstream signalling and the signal transducer and activator transcription factor (JAK STAT) mechanisms. Moreover, the rising oestrogen inhibits insulin receptor function to directly cause insulin resistance and hyperinsulinaemia (Hilf and Crofton, 1985; Gonzalez *et al.*, 2002; Garcia-Arencibia *et al.*, 2005).

In turn, the increasing insulin level attenuates STAT 3 to create even more leptin resistance (Banks *et al.*, 2000; Kellerer *et al.*, 2001; Fujita *et al.*, 2003; Ishida-Takahashi *et al.*, 2006), and increases arcuate neuropeptide Y release to stimulate more unnecessary eating (Insulin Upregulates Arcuate NPY Release); even to the extent of unpalatable gorging.

The synergistic action of leptin in the presence of increased insulin directly targets the corpus luteum (Brannian *et al.*, 1999), which impairs fertility, reduces progesterone output, increases relative oestrogen excess and stimulates increased follicle stimulating hormone (FSH) (Arnaoutoglou *et al.*, 2008; Nakamura *et al.*, 2009), which in combination further upregulate p450 aromatase.

Fig. 1



The role of oestradiol, leptin, cortisol and insulin in the pathogenesis of disease. Carbs, refined carbohydrates; E2, estradiol; ER-α, oestrogen receptor; HSD, hydroxysteroid dehydrogenase; I, insulin; IR, insulin resistance; L, leptin; LR, leptin resistance; XE, xeno-oestrogens.

In essence, the complex synergies between oestradiol, leptin, insulin and cortisol are directed towards the cyclic upregulation of p450 aromatase in adipose cells, uterine cells, prostate cells and breast cells, which significantly increases the production of intracellular oestradiol [a measurement that is far more accurate than serum oestradiol concentrations (Lonning and Geisler, 2008), as intracellular oestradiol levels can be 10–50 times higher than serum concentrations (Van Landeghem *et al.*, 1985)] to increase ER-α stimulation (Cohen, 2008), to stimulate cell growth in breast and prostate tissue, to increase leptin levels (Yi *et al.*, 2008) and to increase subcutaneous fat deposition and insulin resistance (Shin *et al.*, 2007).

The rising oestradiol (Revillion *et al.*, 2006) and insulin (Ishida-Takahashi *et al.*, 2006) levels impair leptin receptor function, and in turn, the resultant hyperleptinaemia (Hennige *et al.*, 2006), and unopposed oestradiol (Gonzalez *et al.*, 2002) subsequently impair insulin receptors, which only serves to create more insulin and more leptin, and so on; and so the vicious circles turn faster as their synergistic actions insidiously escalate.

As fat deposition increases – the more leptin and oestradiol concentrations increase – the faster the progression from overweight to obesity. When the fat cells reach maximal size, the oestradiol and leptin stimulate ectopic fat deposition to induce fatty liver and intramuscular lipid storage (Dyck *et al.*, 2006; Daghestani *et al.*, 2007). They increase noradrenaline formation, sympathetic activity (Pausova, 2006), IL-6 and TNF-α to increase vascular resistance, sodium retention and to induce hypertension (Bogaert and Linas, 2009), and they mediate inflammatory reactions to produce hepatic C-reactive protein (Bastard *et al.*, 2006), endothelial inflammation, atherosclerotic change (Knudson, 2007) and heart disease (Martin *et al.*, 2008; Lieb *et al.*, 2009).

Although xeno-oestrogens are relatively weak (Pugh and Moore, 1998), their cumulative exposure in humans from food, water, plastics, pharmaceuticals and cosmetic products synergistically increase p450 aromatase expression (Kinoshita and Chen, 2003; Laville *et al.*, 2006) to act as an initiator of significantly raised intracellular oestrogen production in adipose (Newbold *et al.*, 2008), uterine, prostate and breast tissue. Although oestradiol and DDT [1,1,1,trichloro-2,2-bis[chlorophenyl]ethane] both increase the growth of MCF-7 human breast cancer cells, oestradiol is 200–300 times more potent (Dees *et al.*, 1997).

As such, rather than merely adding to the oestrogenic load, xeno-oestrogens upregulate aromatase to produce much more, highly potent, intracellular oestradiol, which in turn initiates, promotes and exacerbates oestrogenic growth disorders, and when symptoms persist, disease commences.

Oestrogenic disease

Obesity

Obesity is associated with diabetes, heart disease, breast cancer, Alzheimer's disease, hysterectomy frequency and prostate cancer.

Oestrogen increases the deposition of ectopic fat in liver and muscle, visceral fat in and about organs, and subcutaneous fat accumulation especially on the hips, upper thighs and lower abdomen. The amount of abdominal fat is proportional to its amount of aromatase, the intracellular enzyme that converts testosterone (and ASD) to oestradiol (and oestrone), which in essence increases endogenous oestrogen levels at the expense of testosterone levels.

As the increasing fat cells make more oestradiol (Carr and Bradshaw, 2005), they increase their leptin output (Tanaka *et al.*, 2001), which in turn upregulates aromatase, drives insulin and leptin resistance and stimulates the production of more cortisol.

In essence, fat cells make leptin and oestrogen. Leptin, insulin, cortisol and oestrogen all increase aromatase activity. In turn, leptin and oestrogen increase fat deposition and inhibit insulin receptors. So, the body compensates by making more insulin, which in turn increases oestrogen receptor number and activity (Kaaks, 2005).

The increased oestrogen, increased insulin and raised stress hormone cortisol directly cause leptin receptors to fail – in other words, the satiety hormone leptin is not recognized by the receptors, as if no leptin was present – so in the absence of satiety, the body is stimulated to eat more high-carbohydrate, low-nutrition, insulin-provoking foods, which deposit even more fat, with even higher aromatase (Catalano *et al.*, 2003) activity, which makes more leptin and more oestrogen to deposit more fat, which makes more oestrogen, which increases leptin, and increases insulin and increases cortisol to make more fat, and so on.

Obesity is associated with increased oestrogen production, and body mass index (BMI) is strongly correlated with each of the oestrogens in obese postmenopausal women (Key *et al.*, 2003).

Obesity and subcutaneous fat deposition are associated with an increased ER-α to ER-β ratio (Shin *et al.*, 2007); in turn, higher fat percentages and increased hip circumferences are strongly correlated with increased leptin levels (Ho *et al.*, 1999), hyperinsulinaemia (Borugian *et al.*, 2003) and breast cancer.

Type 2 diabetes

Endogenous oestrogens, exogenous oestrogens and xeno-oestrogens, in concert with leptin, impair insulin receptor function to initiate insulin resistance.

This is the missing link between obesity and diabetes. Low-nutrient, high glycaemic-product carbohydrate diets, ongoing stress, reduced exercise and inherited predisposition only compound the problem.

Raised levels of oestradiol, seen in obesity, oral contraceptive use and injudicious hormone replacement therapy (HRT) promote insulin resistance (Livingstone and Collison, 2002), impair insulin sensitivity (Gonzalez *et al.*, 2002), inhibit human insulin receptor gene expression in a dose and time-dependent manner (Garcia-Arencibia *et al.*, 2005), downregulate insulin receptor function and reduce insulin receptor numbers (Hilf and Crofton, 1985) to directly cause insulin resistance and promote type 2 diabetes.

Even triphasic oral contraceptive use increases insulin levels and reduces insulin sensitivity, such that 10% of women develop impaired glucose tolerance after 6 months of use (Petersen, 2002).

In essence, reactive hyperinsulinaemia, subsequent to the consumption of high glycaemic-product foods, upregulates oestrogen receptors, increases leptin levels, accentuates leptin resistance, upregulates 11β-hydroxysteroid dehydrogenase 1 to increase cortisol production, and upregulates aromatase (Samad, 2007) to lower testosterone, increase oestradiol output, increase fat deposition and directly promote type 2 diabetes – a condition closely associated with increased breast cancer, prostate cancer, obesity and heart disease.

Insulin increases serum leptin levels (Thomas *et al.*, 2000; Falconnier *et al.*, 2003; Manderson *et al.*, 2003; Lindsay *et al.*, 2004), inhibits leptin receptor signalling (Kellerer *et al.*, 2001) and promotes leptin resistance (Banks *et al.*, 2000; Fujita *et al.*, 2003) through attenuation of STAT 3 phosphorylation of JAK-2 on the serine 523 (Ser 523) residue (Ishida-Takahashi *et al.*, 2006).

The leptin receptor, LRb, depends upon tyrosine kinases of the JAK family to mediate intracellular signalling, but phosphorylation of Ser 523 on JAK-2 by insulin itself alters downstream signalling, affects nuclear translocation and ultimately ameliorates target gene expression, and hence causes leptin resistance and subsequent hyperleptinaemia.

The excess leptin further downregulates insulin action to inhibit insulin signalling by promoting the phosphorylation of the serine 318 residue in insulin receptor substrate (Hennige *et al.*, 2006), such that in type 2 diabetes, raised serum leptin levels are directly proportional to the degree of insulin resistance, independent of body mass (Kaur and Zhang, 2005).

Alone, the presence of excess insulin increases the synthesis and activity of oestrogen receptors (Oestrogen Receptors, 1998; Kaaks, 2005) to increase the growth and irritant effects of oestradiol. Even insulin at 10^{-6} mol/l significantly increases breast cancer cell growth (Garnier *et al.*, 2003).

Alone, oestradiol (Santner *et al.*, 1997; Kinoshita and Chen, 2003) and leptin (Catalano *et al.*, 2003; Cirillo *et al.*, 2008) both upregulate aromatase while insulin alone upregulates aromatase 6-fold (Samad, 2007). Together, oestradiol and leptin are synergistic (Dundar *et al.*, 2005), and in combination with insulin, they increase cortisol production 10-fold in women (Dieudonne *et al.*, 2006), which in turn, as mentioned earlier, acts to further upregulate aromatase another 9-fold (Thorton *et al.*, 2006).

So in combination, the raised levels of oestradiol, leptin, insulin and cortisol produce cyclic amplification and upregulation of cytochrome p450 aromatase activity, which acts in the final stage of the steroid cascade to convert testosterone to oestradiol, to raise oestradiol levels and lower testosterone levels.

This pattern of raised free oestradiol levels (Ding *et al.*, 2006) and low testosterone levels (Dhindsa *et al.*, 2004; Osuna *et al.*, 2006) is commonly seen in type 2 diabetes. Although 64% of men with type 2 diabetes have hypogonadism (Kalyani and Dobs, 2007), men with higher testosterone levels have a 42% lower risk of type 2 diabetes (Ding *et al.*, 2006).

Similarly, women with lower free oestradiol levels have an 80% lower risk of developing type 2 diabetes [relative risk (RR) 0.20], and men with lower free oestradiol levels have a 52% lowered risk (RR 0.48) (Ding *et al.*, 2006).

Reversal of this situation by short-term aromatase inhibition has been shown to essentially double testosterone, halve oestradiol and to reduce both serum insulin and leptin levels (Lapauw *et al.*, 2009); in turn, physiological testosterone supplementation improves glucose homeostasis (Boyanov *et al.*, 2003), and decreases insulin resistance and the risk of developing diabetes (Fukur, 2003).

In essence, the production of excess endogenous oestradiol and leptin from abundant adipose tissue increases cortisol, and stimulates simple carbohydrate consumption to increase insulin production. In combination, they significantly upregulate aromatase to produce even more oestradiol, and together with resultant leptin resistance, insulin resistance and excess cortisol, they promote type 2 diabetes, further obesity, heart disease, and oestrogenic breast, uterine and prostate overgrowth conditions.

Anxiety/depression

Although it is normal for humans to suffer stress from unsatisfactory life experiences, it is the neurogenic effect of unopposed oestrogen that creates the tipping point for progressive anxiety and depression.

The normal stress response triggers the release of adrenaline and cortisol, the short and long-acting adrenal

hormones necessary to activate the 'fight or flight' mechanism; however, it is their combined action with oestradiol, itself a highly neuroactive steroid, which increases the frequency of neuronal action potentials, increases synapse numbers, increases dendritic connections and promotes neuronal irritability and noradrenaline release to stimulate heart rate, sweating and blood pressure (Ganong and Lange, 2005), the hallmark of anxiety and hot-flush symptoms.

Unopposed oestradiol in women, and increasing oestradiol in men, together with increased leptin production, increase noradrenaline release (Leal-Cerro *et al.*, 2001), which encourages carbohydrate consumption (Thomas *et al.*, 2000) and insulin release to promote depression and further fat deposition.

Under prolonged stress, cortisol and oestrogen suppress and activate specific reactions in the normal hormone cascade to preferentially increase the production of even more cortisol and more oestrogen, which only serves to exacerbate symptoms further.

Chronic stress increases glucocorticoid production, which mobilizes peripheral fat stores, increases the production of more oestradiol and leptin (Dallman *et al.*, 2007), reduces the ER-α to ER-β ratio to redirect central fat deposition (Thorton *et al.*, 2006) and stimulates further palatable eating and increased insulin release.

In turn, the increased insulin accentuates ER-α function (Oestrogen Receptors, 1998; Kaaks, 2005) to increase leptin production (Yi *et al.*, 2008) and subcutaneous adipogenesis (Iguchi *et al.*, 2008), and in combination they increase aromatase to create more neurogenic oestradiol and anxiety, and further deplete testosterone levels and energy.

Although the natural process of ageing lowers testosterone levels, any associated aromatase upregulation by oestradiol, xeno-oestrogens, leptin, insulin and cortisol only serves to deplete testosterone levels faster (and to increase oestradiol output), such that women in their 40s have half the testosterone of a woman in her 20s (Goldstat *et al.*, 2003), and 60-year-old obese women have half the testosterone of 'normal sized' 60-year-old women (Padero *et al.*, 2002).

Recently, nearly 4000 men with lower testosterone levels associated with ageing revealed an increased incidence of depression, with those in the lowest quartile having a 300% increased risk of depression (Almeida *et al.*, 2008).

Studies that supplement testosterone to restore waning physiological levels show reduced depression (Margolese, 2000), improved mood (Burris *et al.*, 1992), a significant improvement in Hamilton Depressive ratings (Pope *et al.*, 2003) and a reduction of anxiety in male patients (Cooper, 2000). Similarly, postmenopausal women given judicious physiological testosterone supplementation showed return of normal physical and psychological function (Padero *et al.*, 2002), and premenopausal women showed improvement of mood, libido and wellbeing, without detrimental side effects (Goldstat *et al.*, 2003).

Heart disease – cerebrovascular disease

Excess oestrogen, reduced testosterone, increased cortisol, raised insulin levels and accentuated adrenergic responses seen in obesity, diabetes and anxiety, all contribute to increase the incidence of hypertension, myocardial infarction and cerebrovascular accidents.

Excess energy intake and subsequent fat storage increases leptin and endogenous oestradiol production, and reduces testosterone levels through aromatase activation to facilitate the formation of large dysfunctional adipoctyes that produce angiotensin, leptin and proinflammatory cytokines, which stimulate ectopic fat deposition in the skeletal muscle and liver sites (Pausova, 2006), activate hepatic C-reactive protein to promote cardiovascular disease (Bastard *et al.*, 2006), activate sympathetic drive, increase vascular resistance and increase sodium retention to produce obesity-related hypertension (Bogaert and Linas, 2009).

Leptin affects endothelial function and coronary circulation (Knudson, 2007) to induce atherosclerotic disease, and as leptin resistance increases, so does the risk of heart failure, coronary heart disease (CHD), cerebrovascular disease and overall mortality (Lieb *et al.*, 2009). Although oestrogen is associated with an improved lipid profile and has been long-considered atheroprotective, increased local oestradiol production and aromatase expression have now been identified in fibroatheromatous placques, adjacent smooth muscle and in thickened human aortic intima (Murakami *et al.*, 2001), which serve to facilitate plaque formation, intimal disruption and to increase thromboembolic risk.

Increased FSH, increased leptin and preexisting unopposed oestradiol also increase CHD risk in surgically induced and physiological menopause (Verhoeven *et al.*, 2009).

Oestrogen has been controversially associated with an increased risk of thromboembolism, progressing to coronary occlusion, cerebrovascular infarcts and pulmonary emboli, for years. The Women's Health Initiative Study of 2002 (Anderson *et al.*, 2002) found long-term combination conjugated equine oestrogen plus medroxyprogesterone acetate HRT use to be associated with a 29% increase in heart attack, a 41% increase in stroke and twice the risk of serious blood clots. Although recent follow-ups suggest that transdermal HRT application is safer than oral dosing, nevertheless, the National Institute of Health and the Food and Drug Administration state that HRT should not be used to prevent CHD, as it does not reduce the incidence of coronary artery

disease or slow the progression of established artery disease (Lauer, 2008), that it increases the risk of stroke at any time, and that oral HRT can double the risk of thromboembolism in the first year of use (Canonico *et al.*, 2008).

Leaving HRT aside, increasing leptin, cortisol, insulin, xeno-oestrogen exposure, and increasing oestradiol itself, maintain ongoing aromatase upregulation to further increase oestradiol and to significantly deplete circulating free testosterone levels.

An independent inverse relationship exists between low levels of testosterone and the presence of atherosclerosis in men (Murakami *et al.*, 2001; Hak *et al.*, 2002) and coronary artery disease in women (Kaczmarec *et al.*, 2003), the effects of which are reversed by physiological testosterone supplementation, which increases coronary flow and produces coronary artery dilatation (Webb *et al.*, 1999), improved angina threshold and exercise tolerance (Channer and Jones, 2003), improved muscle strength, and generally slowed the ageing process (Allen *et al.*, 2007), without deleterious effects.

Dementia and Alzheimer's disease

The incidence of Alzheimer's disease, the most common form of dementia, is currently doubling every 20 years (Ferri *et al.*, 2005).

High serum oestradiol levels in women (Ravaglia *et al.*, 2007) and low testosterone levels in men (Pike *et al.*, 2006) are independent predictors for dementia and Alzheimer's disease.

In men and women, obesity and raised BMI are associated with an increased risk of Alzheimer's disease (Luchsinger and Gustafson, 2009) and an accelerated rate of brain atrophy, such that obese nondementia individuals suffered 8% more brain atrophy over 5 years than lean individuals (Raji *et al.*, 2009).

The raised endogenous oestradiol of obesity and the hyperinsulinaemia of type 2 diabetes are closely linked to a significant increase in the risk of Alzheimer's disease in men and women (Luchsinger and Gustafson, 2009), whereas oestrogen-containing HRT essentially doubled the incidence of dementia in the Women's Health Initiative Memory Study (Craig *et al.*, 2005).

As such, the cumulative effect of upregulated aromatase, increased unopposed endogenous oestradiol and any xeno-oestrogen exposure, together with the consequential reduction of free testosterone associated with aromatase conversion, raised sex hormone binding globulin levels and a naturally lowered output, directly induce progressive β-amyloid accumulation and consequent dementia, in both men and women.

Interestingly, while raised endogenous oestrogen and prescribed HRT oestrogen both increase Alzheimer's disease, androgen depletion also accelerates the abnormal accumulation of β-amyloid in specific areas of the brain (Pike *et al.*, 2006) to produce Alzheimer's disease-like neuropathy (Rosario *et al.*, 2006). Lower free testosterone levels, a better marker of androgen loss, are associated with reduced processing speed and impaired executive function, whereas higher testosterone levels are associated with improved cognitive function (Muller *et al.*, 2005).

Significantly, the restoration of physiological levels of testosterone in hypogonadal men reversed the degree of dementia while those on placebo continued to deteriorate (Tan and Pu, 2003).

Benign uterine disease, endometrial and ovarian cancer

Oestrogenic compounds promote endometrial proliferation, and promote progression to endometrial hyperplasia, atypia and neoplasia (Vainio *et al.*, 1992).

Endometrial cancer and exogenous oestrogens have been linked since 1951, such that conjugated equine oestrogens and oestradiol both confer an 8-fold increase in the RR of endometrial cancer (Beresford, 1997). Even physiological levels of oestradiol and oestrone, without the opposing effects of progesterone, have been shown to significantly increase the risk (Overall Evaluation of Carcinogenicity, 1987).

Unopposed oestradiol stimulates cyclo-oxygenase-2 to increase the formation of prostaglandin-E2, which promotes aromatase expression in endometrial tissue (normally devoid of aromatase activity), stimulates dysfunctional endometrial growth in endometriosis (Bulun *et al.*, 2005) and increases the production of tumourigenic, hydroxylated oestradiol metabolites, which promote the formation of uterine leiomyomata (Leihr *et al.*, 1995). The 4-hydroxyoestrogens form unstable adducts to induce DNA damage, and transform mutations to cause endometrial and ovarian cancer (Emons *et al.*, 2002), such that ovarian cancer cells display increased cell proliferation and reduced apoptosis, even at physiological concentrations of oestradiol (Seeger *et al.*, 2005). A dose-dependent relationship exists between annual exposure to oestrogenic HRT and an increased risk of ovarian cancer (Greiser *et al.*, 2007); similarly, any exposure to oestrogenic HRT increases the risk of ovarian cancer by 50% (Zhou *et al.*, 2008). In fact, the World Health Organization International Agency for Research and Cancer, which included oestrogenic HRT and oestrogenic oral contraception on their 2005 carcinogenic list, added the oestrogenic HRT/ovarian cancer relationship to its known carcinogenic agent list in 2009 (Grosse *et al.*, 2009).

The use of HRT increases the risk of developing and dying of ovarian cancer by 20%, and increases the total

incidence of endometrial, breast and ovarian cancer, which represent 40% of all UK cancers, by 63% (Beral, 2007).

Benign prostatic hyperplasia

Oestrogens initiate and promote benign prostatic hyperplasia (BPH) (Hammarsten *et al.*, 2009) through upregulation of prostatic aromatase (Risbridger *et al.*, 2003) to raise intracellular oestradiol levels, increase subsequent 3,4-catechol oestradiol formation (Leihr *et al.*, 1995) and to promote periurethral prostatic adenomatous hyperplasia typically in the transitional zone.

Although BPH has long been attributed to an excess of testosterone, there is no clinical evidence that the incidence of BPH or even prostate cancer increases with testosterone replacement therapy (Morley, 2000); in fact, multiple studies have failed to show any exacerbation of symptoms attributable to BPH during testosterone supplementation (Rhoden and Morgentaler, 2004).

Although it is quite paradoxical to consider oestrogen, and not testosterone, as the cause of prostate disease, it is nevertheless quite understandable, when one considers that prostate disease typically occurs at a stage in a man's life when his testosterone levels are low.

> If testosterone is the cause of prostate cancer, then we should have got it when we were young men, and not at a time in our life when our testosterone is at its lowest (Williams, 2006).

Prostate cancer

Prostate cancer, detected in 30% of 50 year-old men in random autopsy studies (Bosland *et al.*, 2002), is now the most common male cancer in many western countries.

Prostate cells, both normal and malignant, contain all the essential enzymes necessary to convert dehydroepiandrosterone to oestradiol, in particular 17β-hydroxysteroid dehydrogenase and aromatase, and they also exhibit ER-α and ER-β, with ER-α being essentially proliferative, and ER-β in the main inhibitory (Carruba, 2007). Testosterone is metabolized by 5α-reductase to form the more potent androgen, dihydroxytestosterone, which in turn activates the androgen receptor.

It seems that the principal role in cell proliferation and metaplastic change rests with the prostatic activation of 17β-hydroxysteroid dehydrogenase, and the expression and upregulation of aromatase, both of which increase intracellular prostatic oestradiol levels (through estrone conversion and androgen aromatization, respectively) to produce divergent activation of the proliferative ER-α more than the inhibitory ER-β (Carruba, 2006).

ER-α activation is essential for BPH, inflammation and prostate cancer to occur while ER-β stimulation reduces prostatic hypertrophy, inflammation and prostate cancer (Ellem and Risbridger, 2007). A reduction in ER-β expression, and hence reduced growth inhibition, has been noted in prostate cancer (Bardin *et al.*, 2004), with some studies revealing that ER-β expression progressively declines in localized prostate cancer, as Gleason scores increase from prostatic intraepithelial neoplasia to advanced prostate cancer (Prins and Korach, 2008).

The days of blaming testosterone alone for prostate cancer have passed. Although it may play a minor role through androgen receptors, it is intracellular oestradiol that directly induces the proliferation of aberrant prostatic basal cell hyperplasia to promote the formation of squamous metaplasia (Risbridger *et al.*, 2001, 2007). The ratio between free testosterone and free oestradiol seems to determine both the extent of aromatase upregulation through nuclear and nonnuclear ERs, and the degree of ER-α stimulation (Prins and Korach, 2008).

The weight of evidence postulates that leptin, xenooestrogens, cortisol and oestradiol all upregulate ER-α, aromatase and 17β-hydroxysteroid dehydrogenase to induce proliferative prostatic metaplasia and neoplasia, just as they do in breast carcinogenesis.

Obesity and increased leptin increase the incidence and aggressiveness of prostate cancer (Mistry *et al.*, 2007), and men with a BMI above 30 have a 78% increased risk of high-grade prostate cancer, with a Gleason score above 8 (Gong *et al.*, 2006).

The synergistic action of insulin and leptin, seen in men with higher insulin and waist–hip ratios, have an 8.55-fold increased risk of prostate cancer while a raised insulin alone confers a 2.56-fold increased risk (Hsing *et al.*, 2001).

Raised free oestradiol levels also increase prostate cancer risk (Gann *et al.*, 1996), as do lipophilic, liposoluble, oestrogenic endocrine disruptors, pesticides and environmental carcinogens (Imigaray *et al.*, 2007; Prins, 2008), which include Agent Orange (Chamie *et al.*, 2008), shown to cause prostate cancer sooner in exposed men, with a mean time from exposure to diagnosis of 407 months, and to double the aggressiveness of the cancer, with Gleason scores above 8.

Apart from direct ER activation, the formation of DNA adducts from oxidized electrophilic oestradiol metabolites, in particular estradiol-3,4-quinone, and the generation of excessive reactive oxidizing species, directly induce oxidative modification to DNA bases to form 8-hydroxy-2′-deoxyguanosine and 5-hydroxymethyl-2′-deoxyuridine, known prostatic carcinogens (Han *et al.*, 1995; Leihr, 1997).

Low testosterone levels, rather than high testosterone levels, are associated with prostate cancer (Schatzl *et al.*, 2001) with little compelling evidence to suggest that high testosterone, or testosterone supplementation, increases prostate cancer risk (Prehn, 1999; Morley, 2000; Morales, 2002; Rhoden and Morgentaler, 2004).

Lower free testosterone levels are correlated with positive prostate biopsies and high Gleason scores (Gustafsson *et al.*, 1996; Hoffman, 2000; Schatzl *et al.*, 2001), whereas men with higher free testosterone levels have a lower risk of developing prostate cancer (Stattin *et al.*, 2004).

Breast cancer

Anything that upregulates the expression or activity of cytochrome p450 aromatase (or increases the formation of catechol DNA adducts) will increase the risk of breast cancer, whether it be caused by physiological levels of oestradiol, unopposed by progesterone, increased leptin levels, as seen in obesity and leptin resistance, reactive hyperinsulinaemia attributable to injudicious consumption of sugars and high-glycaemic foods, raised cortisol levels associated with chronic stress, or xeno-oestrogen exposure innocently consumed in food, water and skin products or prescribed as medication for humans, stock and farm produce.

Physiological unopposed oestradiol levels and breast cancer: The carcinogenic role of 17β-oestradiol has been confirmed – it induces neoplastic transformation in human breast cancer cells (Russo and Russo, 2006), promotes the growth of breast cancer cells *in vivo* and *in vitro* (Dees *et al.*, 1997), 1 nmol/l of 17β-oestradiol induces a 7–13-fold increase in human breast cancer cell numbers (Gupta *et al.*, 1998) and significantly increases the risk of breast cancer (Berrino *et al.*, 1996; Rock *et al.*, 2008), such that unopposed oestradiol alone confers an increased (RR 2.58) risk of breast cancer in post-menopausal women (Key *et al.*, 2002). Even the comparison of women in the upper normal oestradiol range to the lower normal range, revealed an increased RR of 3.3 (Missmer *et al.*, 2004), and in ER-positive breast cancer patients who had never received HRT, those women in the upper quarter of the normal physiological oestradiol range had an almost 5-fold increased risk, compared with those in the lower quarter normal range (Missmer *et al.*, 2004).

Obesity, BMI, percentage fat (Petrelli *et al.*, 2002; Borugian *et al.*, 2003; Key *et al.*, 2003), type 2 diabetes and insulin resistance (Oestrogen Receptors, 1998; Muti *et al.*, 2002; Garnier *et al.*, 2003; Harvard Nurses Health Study, 2003; Kaaks, 2005; Mawson *et al.*, 2005; Ishida-Takahashi *et al.*, 2006), all increase breast cancer risk and mortality. Leptin levels increase remarkably with increasing fat percentage (Daghestani *et al.*, 2007), and so does the ER-α to ER-β ratio (Shin *et al.*, 2007). Leptin interferes with STAT 3 signalling and activates ER-α in malignant breast tissue (Sulkowska *et al.*, 2006); it doubles FSH to upregulate aromatase (Arnaoutoglou *et al.*, 2008), and it interferes with insulin signalling (Kaur and Zhang, 2005) by directly promoting phosphorylation of Ser 318 in insulin receptor substrate to downregulate insulin receptor action (Hennige *et al.*, 2006).

In effect, the increased leptin creates an excess of ineffective insulin, which attenuates STAT 3 phosphorylation, impairs leptin receptor ObR-L function (Banks *et al.*, 2000) and phosphorylates Ser 523 on JAK-2 to inhibit further downstream signalling, nuclear translocation, and receptor gene expression to ultimately amplify the hyperleptinaemia (Ishida-Takahashi *et al.*, 2006), and accentuate the insulin resistance and leptin resistance cycle to increase the risk, incidence and overall mortality of breast cancer.

Oestradiol itself upregulates aromatase activity (Santner *et al.*, 1997), and leptin alone increases aromatase expression (Catalano *et al.*, 2003) to increase intracellular microenvironment oestradiol levels, which induce ER-α (Catalano *et al.*, 2004) and transactivate epidermal growth factor receptors to promote breast cancer invasion and migration (Cirillo *et al.*, 2008). The intracellular levels of aromatase (Lonning and Geisler, 2008) and oestradiol (Van Landeghem *et al.*, 1985) reflect the highly oestrogenic microenvironment of breast cancers better than plasma levels, with intracellular levels being 10–50 times higher than plasma levels.

The cyclic amplification of aromatase by leptin and oestradiol is highlighted by their capacity to increase 11β-hydroxysteroid dehydrogenase expression (Catalano *et al.*, 2003), and so increase intracellular cortisol production (Dieudonne *et al.*, 2006), which in turn upregulates aromatase (Thorton *et al.*, 2006), the product of which positively feedsback onto 11β-hydroxysteroid dehydrogenase to complete the cycle, and also increases fat deposition and hence leptin production to upregulate aromatase, increase insulin resistance (Dallman *et al.*, 2007) and stimulate further growth. Leptin and oestradiol combine to potentiate ER-α activation (Catalano *et al.*, 2004) and to enhance cell cycle progression of breast cancer cells (O'Neil *et al.*, 2001; Mawson *et al.*, 2005).

Significantly, unopposed, endogenous, 17β-oestradiol has been shown to induce human breast epithelial cell genomic alterations, at the same locations as other known carcinogens, such as diethylstilboestrol and benzopyrene (Russo *et al.*, 2001). Even at concentrations of 0.1 nmol/l, 17β-oestradiol, 4-hydroxyoestradiol and 16-hydroxyoestradiol display proliferative growth effects in human breast cancer cells (Seeger *et al.*, 2006).

The carcinogenic properties of oestradiol and oestrone are highlighted by their capacity to form catechol oestrogen-3,4-quinones, the ultimate carcinogenic metabolites of excess endogenous and exogenous oestrogens.

Oestrogens can be converted to electrophilic metabolites, particularly the catechol oestrogen-3,4-quinones, oestradiol-3,4-quinone and oestrone-3,4-quinone, which react with DNA to form the depurinating adducts, 4-$OHE_2(E_1)$-1-N3adenine and 4-$OHE_2(E_1)$-1-N7guanine,

which provoke error-prone base excision repair and mutation formation that initiates breast cancer in women and prostate cancer in men from unopposed endogenous oestrogen and synthetic oestrogens (Cavalieri and Rogan, 2006). The 4-hydroxylation pathway producing catechol oestrogen-3,4-quinone is responsible for the genotoxic effects leading to oestrogen-induced cancer (Cavalieri and Rogan, 2004), such that men with prostate cancer and women with breast cancer have increased oestrogenic depurinating adducts in their urine, when compared when healthy men and women (Cavalieri and Rogan, 2006).

Xeno-oestrogens and breast cancer: Pharmacological doses of oestrogen and exposure to environmental oestrogen-like xenoestrogens have been proven to be carcinogenic, teratogenic and embryotoxic (Baan *et al.*, 1999). Environmental oestrogen-like chemicals increase the aromatase sensitivity and expression (Risbridger *et al.*, 2007) of ER-α receptors, supporting the critical role of aromatase upregulation in breast cancer development (Kinoshita and Chen, 2003).

An increased risk of breast cancer has been established with the use of oral contraceptives (Breast Cancer Hormonal Contraceptives, 1996; De Benedetti *et al.*, 1996; Schneider *et al.*, 2005) and HRT (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Michaeli *et al.*, 2004; Fournier *et al.*, 2005). A 26% increased risk was found in the 18 000 postmenopausal women in the Women's Health Initiative prospective study (Anderson *et al.*, 2002), and a 66% increased risk of incident and fatal breast cancer was determined in the Million Women Study (The Million Study Collaborators, 2003). Breast cancer risk has been found to persist for 3 years after cessation of HRT (Heiss *et al.*, 2008).

In June 2005, the WHO International Agency for Research and Cancer classified combination hormone contraception (the oral contraceptive pill) and combined menopausal therapy (HRT) as carcinogenic (Cogliano *et al.*, 2005), and their carcinogenic properties were confirmed by the group in 2009 (Bouvard *et al.*, 2009).

Endocrine disruptors mimic the action of sex hormones (Nilsson, 2000). In particular, the man-made oestrogenic endocrine disruptors, politely referred to as environmental chemicals, exhibit potent, lipophilic, fat-soluble, long half-life, high ER-binding properties that facilitate their spread and residual accumulation through food chains to create an almost irretrievable, global ecotoxic health crisis. This is a human health burden so massive that it significantly contributes to human suffering and loss of productivity worldwide (Earth Summit, 1992). A pandemic so grave and accelerating in nature that it will, if not courageously contained, compromise human fertility and ultimately human survival.

The common commercial chemicals, bisphenol A, butyl benzyl phthalates, dioxin 2,3,7,8-TCDD, cadmium, arsenicals, nonylphenol, octophenol; and the PCB industrial chemicals, endosulfan, lindane, parathion, dieldrin, and DDT insecticides, hexachlorobenzene, maneb and tributyltin fungicides and 2,4,-D, 2,4,5,-T and atrazine herbicides, to name a few, are all endocrine disruptors (Bouvard *et al.*, 2009).

Even ultraviolet filters are a class of endocrine active chemicals, in particular 4-methyl-benzilidine camphor and octyl-methoxycinnamate, shown to display dose-dependent oestrogenic action in MCF-7 human breast cancer cells, and to affect oestradiol-regulated genes in the prostate and uterus (Schlumpf *et al.*, 2004).

Although both DDT and endogenous oestradiol (17β-oestradiol) promote breast cancer growth *in vitro* and *in vivo* (Dees *et al.*, 1997), it should be appreciated that oestradiol is 200–300 times more potent, being capable of inducing change at one femtomol (0.000 000 000 000 001M) (Watson *et al.*, 2008). The extent of human exposure to long-term, low-dose pesticides and their insidious capacity to significantly upregulate intracellular oestradiol production is highlighted by the fact that DDT is applied to crops in litres, and pesticides are applied to edible produce, the skin of animal stock and farm workers, in grams.

In particular, it is not the total accumulated oestrogenic load that has tipped the balance over the last 20 years, it is the intense upregulation of aromatase (through our long-term food and corporate exposure to endocrine disruptors, and the synergistic cyclic amplification of oestradiol, leptin, cortisol and insulin) that has increased intracellular oestradiol production and oestradiol catechol formation, proven to induce cell changes from hypertrophy to neoplasia. Oestrogenic disorders exhibited worldwide today, in the form of obesity, type 2 diabetes, anxiety and depression, cardiovascular disease, benign uterine and prostatic hyperplasia, uterine and prostate cancer and breast cancer (not to mention precocious puberty, genetic malformations and rising infertility), will only increase in incidence, if change is not forthcoming.

Symptom control and disease prevention

In the final stage of the steroid cascade, cytochrome p450 aromatase converts testosterone to oestradiol. As such, any compound that upregulates aromatase will increase intracellular bioactive oestradiol concentrations, and increase the incidence of oestrogen-mediated growth disorders, including obesity, diabetes, uterine overgrowth, BPH, breast cancer and prostate cancer.

Conversely, aromatase inhibition has been shown to lower oestradiol levels by 62%, and to reduce fasting insulin levels by 37% and circulating leptin levels by 24% (Lapauw *et al.*, 2009).

The application of dosed quantities of transdermal progesterone is a cost-effective means of aromatase

inhibition, readily available in most economic regions. Furthermore, it attenuates the deleterious effects of unopposed oestrogen, improves leptin and insulin receptor function, downregulates ER-α action, reduces the incidence of breast cancer and provides a substrate for testosterone synthesis, necessary to naturally restore the waning levels seen in osteoporosis, Alzheimer's disease, depression and type 2 diabetes.

Although oestradiol (Dieudonne *et al.*, 2006), leptin (Dundar *et al.*, 2005; Dieudonne *et al.*, 2006), insulin (Samad, 2007), cortisol (Brueggemeier *et al.*, 2001), FSH (Arnaoutoglou *et al.*, 2008) and xeno-oestrogens (Laville *et al.*, 2006; Nakanishi, 2008; Prins 2008) all upregulate aromatase, physiological levels of progesterone downregulate aromatase (Kinoshita and Chen, 2003), decrease leptin secretion (Coya *et al.*, 2005) and improve leptin receptor expression and signalling (Revillion *et al.*, 2006).

Oestradiol upregulates ER-α, whereas progesterone reduces ER number 5-fold (Iosif and Batra, 1994), and reduces nuclear ER count and activity (Fuentes *et al.*, 1990).

Normal progesterone levels reduce breast cancer risk by 88% (RR 0.12) in premenopause (Kaaks *et al.*, 2005), and halve the risk (RR 0.5) in postmenopausal women (Michaeli *et al.*, 2004). Progesterone also inhibits human breast cancer cell growth by upregulation of p27 gene (Gizard *et al.*, 2005); it downregulates breast cancer IGF-1 growth factor (Yamada *et al.*, 2004), which has been shown to act with leptin to increase invasion and migration of breast cancer (Saxena *et al.*, 2008); and progesterone action can improve the prognosis of those with primary breast cancer (Revillion *et al.*, 2006).

Synthetic progestins increase breast cancer risk (Michaeli *et al.*, 2004) and upregulate aromatase (Xu *et al.*, 2007), and increase leptin (Sagsoz *et al.*, 2009) while natural progesterone does not (Michaeli *et al.*, 2004). Never confuse natural human hormones with synthetic, similar-shaped, patented hormones, which have different affinities for receptors and binding globulins, and rarely any capacity for natural metabolic action.

Increased intracellular oestradiol and reduced free testosterone levels are the result of upregulated aromatase. Low testosterone levels are closely related to type 2 diabetes, obesity, prostate cancer, osteoporosis, anxiety and depression, heart disease and accelerated ageing.

The restoration of physiological levels of testosterone (with the appropriate aromatase blockade) increases muscle size, reduces abdominal fat and slows the ageing process (Allen *et al.*, 2007). Although oestradiol increases the progression of Alzheimer's disease (Craig *et al.*, 2005; Ravaglia *et al.*, 2007), testosterone has been shown to improve cognitive performance (Muller *et al.*, 2005) and to reverse its effects (Tan and Pu, 2003). Testosterone reduces the incidence of insulin resistance and metabolic syndrome (Fukur, 2003), and improves leptin function (Söderberg *et al.*, 2001; Horenburg *et al.*, 2008).

Bearing in mind the inverse relationship between low testosterone levels and atherosclerosis in men (Hak *et al.*, 2002) and women (Kaczmarec *et al.*, 2003), testosterone supplementation increases coronary blood flow and coronary artery dilatation (Webb *et al.*, 1999), increases exercise tolerance and reduces angina (Channer and Jones, 2003).

Psychologically, low testosterone has been shown to triple depression in men (Almeida *et al.*, 2008). Physiological testosterone supplementation in men improves mood (Cooper, 2000; Margolese, 2000), increases Hamilton depressive rating scores (Pope *et al.*, 2003) and improves libido and erection quality (Burris *et al.*, 1992), without any adverse association with BPH or prostate cancer (Morley, 2000). In fact, higher free testosterone levels are associated with reduced prostate cancer incidence and aggressiveness (Schatzl *et al.*, 2001; Stattin *et al.*, 2004).

Women aged in their 40s have half the testosterone of those in their 20s (Goldstat *et al.*, 2003). Testosterone supplementation restores physical and psychological function (Padero *et al.*, 2002), and improves mood and wellbeing (Goldstat *et al.*, 2003), without adverse effects.

The restoration of physiological hormone levels requires accurate dosing, whether it be insulin, thyroxine, progesterone or testosterone. If a particular human hormone is deficient, use the very same hormone at an exact dose necessary to restore the natural physiological level.

Unfortunately, the use of vitamins, herbs and massage to 'balance hormones' is unacceptable, as they will never restore natural hormone levels; similarly, the prescription of a 'one dose fits all' hormone is medically inappropriate, bearing in mind the widespread individual variation in body fat percentages, bioavailable oestrogen levels, current medications and coexisting conditions in the community. However, the prescription of an appropriate dose of progesterone, together with dietary modification to avoid the consumption of high glycaemic product, high insulin-producing foods, and some objective exercise advice is easily achievable by most caring medical practitioners – a cost-effective, high-yield, preventative measure that will reduce wasted expenditure and improve global health.

Moderate medium exercise improves insulin action (Park *et al.*, 2005; Franks *et al.*, 2007), and in leptin resistance, it improves both insulin and leptin function through improved signal transduction (Dyck, 2005; Flores *et al.*, 2006), such that even short-term exercise and diet programmes have been shown to improve hormone function (Miller *et al.*, 2008).

The importance of a balanced regimen incorporating dietary modification, moderate aerobic exercise, avoiding exposure to xeno-oestrogens, and the restoration of physiological progesterone (and in some cases testosterone) levels to counteract the excesses of oestrogen, leptin and aromatase cannot be overemphasized.

Discussion

At a time when governments worldwide are struggling to meet the financial demands of burgeoning health systems, a credible opportunity to resoundingly reduce the incidence of obesity, diabetes, depression, breast cancer and prostate cancer is at hand – an opportunity to improve the diminishing health of nations and to significantly reduce government health expenditure.

The upregulation of aromatase in adipose tissue, breast cells and prostate cells by xeno-oestrogens, the stress hormone cortisol, and insulin from injudicious carbohydrate consumption results in increased intracellular oestradiol and leptin concentrations, both of which further upregulate aromatase to create even more intracellular oestradiol through cyclic amplification.

The peer-reviewed evidence of hundreds of clinical researchers has been integrated to reveal, for the first time, the common link between aromatase upregulation by the synergistic actions of oestrogen, leptin, insulin and cortisol, and the pathogenesis of obesity, diabetes, breast cancer and prostate cancer – the 21st century epidemic and how simple preventative measures, including combined aromatase blockade, dietary modification and exercise, can reduce the global incidence of these diseases.

The significance of how stress, poor diet and xeno-oestrogen exposure combine to significantly increase intracellular oestradiol levels by cyclically upregulating aromatase cannot be underestimated, for it initiates fat deposition, further oestradiol and leptin production, increased anxiety, insulin and leptin resistance, type 2 diabetes and overgrowth conditions of oestrogenic tissues from obesity and uterine/prostate hypertrophy to prostate cancer and breast cancer. This revelation alone will reshape preventative medicine and global health for decades.

Although it is now possible to ameliorate the symptoms of menopause and andropause, and to reduce the risk of individuals developing oestrogenic disease, it is critical that governments acknowledge the deleterious effects that xeno-oestrogen exposure and ultimately cumulative oestrogen levels have upon global health, if we are to prevent the progressive wave of oestrogen-related disease that threatens the future health of nations.

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