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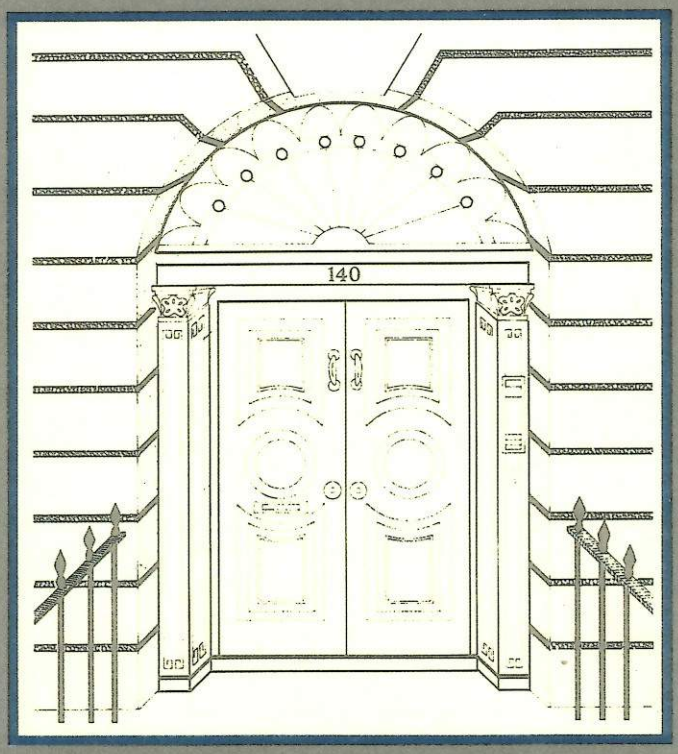

OSTEOPOROSIS

PREVENTION, DETECTION, TREATMENT

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OSTEOPOROSIS: PREVENTION, DETECTION TREATMENT

THE ENDOCRINE & DERMATOLOGY CENTRE sited in London's Harley Street, the heart of Private Medicine, was founded in 1987 by Dr Christopher H Mortimer to make available to patients the latest clinical advances in hormone, biochemical and immunological research in the treatment of related conditions. This present publication in the EDC: Update Series is devoted to the subject of the Prevention, Detection and Treatment of Osteoporosis.

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CONTENTS

1 INTRODUCTION

Osteoporosis ('porous bones') results from loss of the protein (collagen) structure of the bones firstly from the honeycombed inside (the trabecular bone) and then from the smooth outer surface (the cortical bone) leading to premature fracturing (Figure 1).

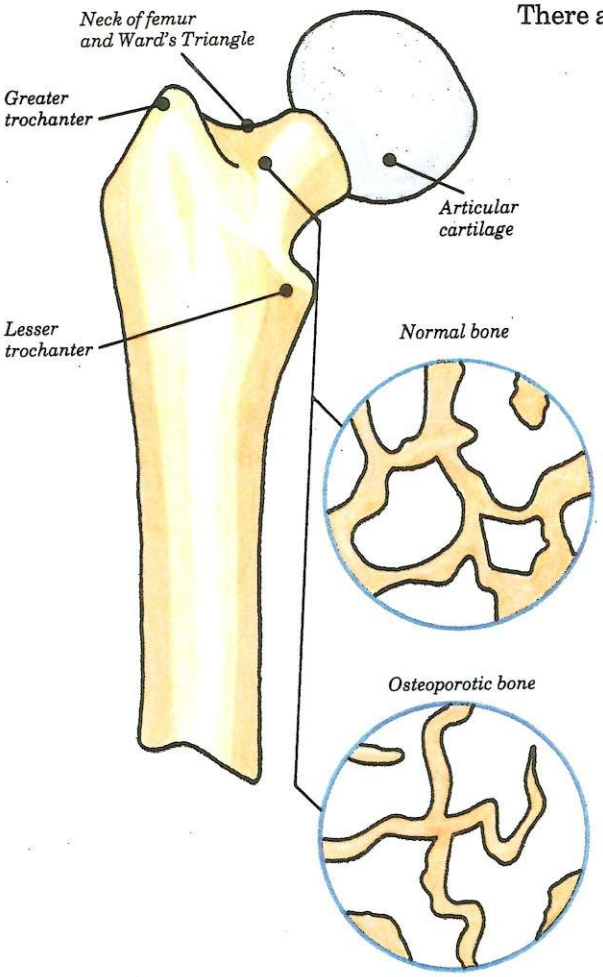

Figure 1. Neck of femur: Thinning and loss of trabecular plates is the most serious feature of Osteoporosis.

There are two main forms of Osteoporosis [1]:

a) The Primary form is divided into: TYPE I which is six times more common in women especially after the menopause with bone loss occuring in all patients. Loss may be from the lumbar spine (lower back) leading to collapse of the vertebrae (Figure 2), loss of height and in the upper spine 'Dowagers Hump' (Figure 3), also from the neck of the femur and from the long bones of the arms and legs with 1 in 4 women sustaining a fracture if untreated; TYPE II which affects twice as many women as men with increasing age (Table 1).

THE TWO PRIMARY TYPES OF OSTEOPOROSIS	TYPE I	TYPE II
Age (years)	51-75	›70
Sex ratio (F:M)	6:1	2:1
Type of bone loss	mainly trabecular	trabecular and cortical
Rate of bone loss	accelerated	not accelerated
Fracture sites	vertebrae (crush) and distal radius	vertebrae (multiple wedge) and hip
Parathyroid function	decreased	increased
Calcium absorption	decreased	decreased
Metabolism of 25-OH Vit D to $1,25(OH)_2$ Vit D	secondary decrease	primary decrease
Main causes	factors related to menopause	factors related to ageing

TABLE 1.

b) The Secondary form is associated with corticosteroid treatment e.g. for asthma, eczema, rheumatoid arthritis and also occurs in patients with thyrotoxicosis (overactive thyroid gland), anorexia nervosa, diabetes mellitus, cirrhosis of the liver (often due to alcohol). Drugs including methotrexate used in the treatment of skin diseases such as psoriasis may precipitate the condition and other illnesses are important contributory factors (Table 2). Despite much medical literature on the subject, it is only now being appreciated that Osteoporosis is a serious medical condition.

SECONDARY CAUSES OF OSTEOPOROSIS
Long term use of corticosteroids
Long term use of anticonvulsants
Drugs e.g. methotrexate
Gastric or small bowel resection
Hyperparathyroidism
Thyrotoxicosis
Anorexia nervosa
Malignant disease e.g. lymphoma
Hypogonadism in men
Hemiplegia
Chronic obstructive lung disease
Mast cell tumour secreting heparin
Intestinal lactase deficiency
Diabetes mellitus
Cirrhosis of liver
Idiopathic juvenile form (cause unknown)
Disuse osteoporosis of arthritis
Post traumatic osteoporosis
Over exercise leading to amenorrhoea
Bone marrow disease and malignant metastases
Late osteogenesis imperfecta

TABLE 2.

The following figures emphasise the extent of the problem:

1. Fracture of the neck of the femur (Figure 4) in women caused more deaths than cancer of the breast and uterus combined in the USA in 1983[2].
2. In 1985 the DHSS recorded 44,000 hospital admissions for hip fractures in England and Wales of whom almost 80% were women and 26,000 were over 75 years of age[3].
3. Of those patients admitted with hip fractures almost 9,000 died while 22,000 became invalids dependent on relatives or the State for their continued existence.
4. Patients with Osteoporosis related fractures permanently occupy 10,000 hospital beds.
5. To the above figures must be added those patients with Osteoporosis who are not counted in the figures since they are not hospitalised but suffer from fractured vertebrae, back pain, fractures of the ribs sometimes just on coughing, wrist, radius and ulna (forearm), tibia and fibula (lower leg), pelvis.
6. The cost to the country has been estimated by one leading expert to be in excess of £1,000,000,000.00 p.a. with a rise of 6% in the total number of affected patients annually.

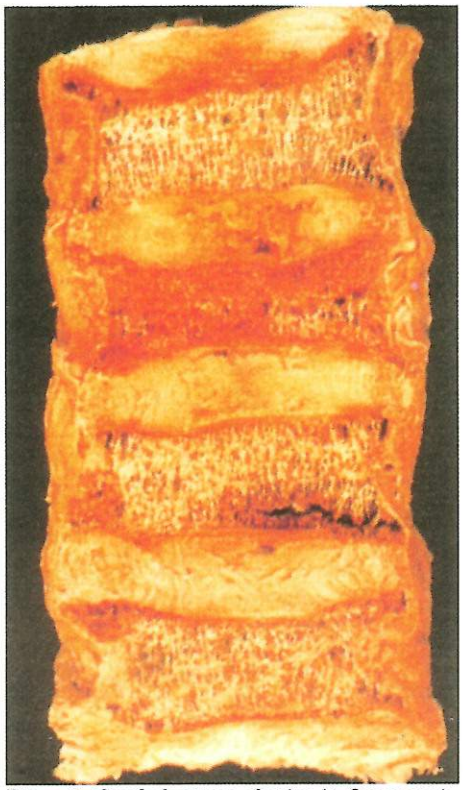

Figure 2. Crush fractures of spine in Osteoporosis. Vertebrae normally 3-4 times height of intervertebral discs. (Reproduced from A Colour Atlas of Bone Disease, V Parsons by kind permission of Wolfe Publishing Limited).

Since an individual woman may lose 40% of her trabecular bone mass and 30% of her cortical bone mass during her life without any symptoms until a fracture occurs, the overwhelming importance of prevention, early detection and treatment must be made a priority[4].

This present publication sets out a review of the latest scientific literature on the subject of Osteoporosis to provide an integrated approach to the alleviation of this disabling condition.

Patients are advised to consult their own General Practitioner or Medical Adviser as to the relevance of the information given to their own particular case history.

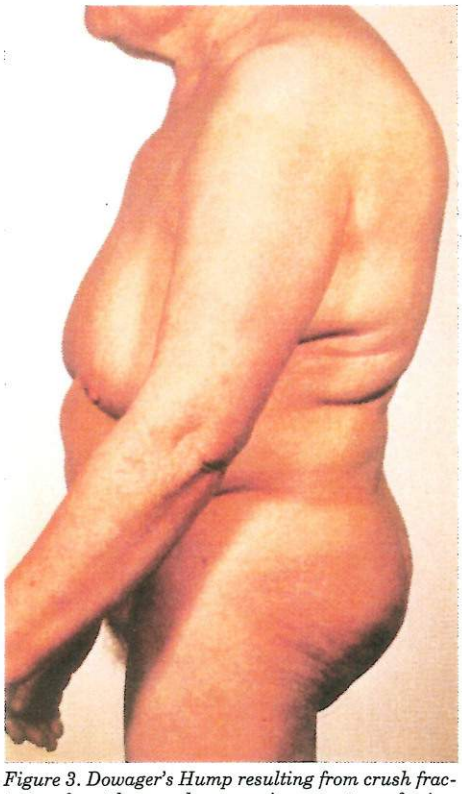

Figure 3. Dowager's Hump resulting from crush fractures of vertebrae and progressive curvature of spine. (Reproduced from A Colour Atlas of Bone Disease, V Parsons by kind permission of Wolfe Publishing Limited).

2 RISK FACTORS IN OSTEOPOROSIS

The major risk factors implicated in the development of Osteoporosis include prolonged inadequate ovarian function (e.g. with irregular, infrequent, scanty periods), early menopause, family history, low calcium and vitamin D intake, insufficient or intermittent sHRT (Table 3).

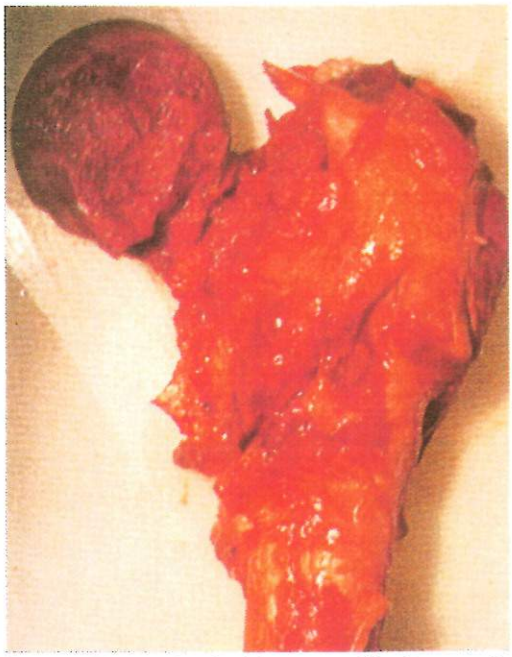

Figure 4. Fractured neck of femur caused by Osteoporosis. (Reproduced from A Colour Atlas of Bone Disease, V Parsons by kind permission of Wolfe Publishing Limited).

Certain conditions can result in a decline in bone formation or an increase in resorption, the result being a loss of bone mass. Anorexia nervosa illustrates one mechanism of action. Malnutrition with a loss of body weight and psychological influences causes the secretion of a brain hormone in the hypothalamus (Gonadotrophin releasing hormone, Gn-RH) to fail leading to lack of stimulation of the pituitary gland to make the hormones (LH and FSH) which normally control the ovaries. Consequently circulating oestrogen levels fall, ovulation fails with low progesterone levels, the periods stop and Osteoporosis begins. However with effective treatment and return of the body weight and oestrogen levels to normal, the loss of bone is reversible[5]. A fall in oestrogens and androgens (male hormones e.g. testosterone) from the adrenal glands also occurs in both sexes with age, with the result that bone is further deprived of those hormones which would normally stimulate its renewal.

Corticosteroid treatment has a powerful effect in causing Osteoporosis reducing bone mass by a combination of malabsorption of calcium, increased bone resorption and calcium loss from the kidney. The process is especially marked in children where retardation of bone growth may occur persisting into adult life.

Heredity and racial factors play an important role with Caucasian and Orientals being particularly susceptible while patients of African origin appear to be protected due to stronger trabeculae and possibly a higher bone mass in young adulthood.

In all of the above specific instances of increased risk factors, being a woman is an additional disadvantage.

MAJOR RISK FACTORS INVOLVED IN OSTEOPOROSIS IN WOMEN
Inadequate ovarian function (e.g. irregular, infrequent, scanty periods, may decline after 30 years of age).
Premature menopause (younger than 46 years of age).
Postmenopausal (increasing risk with age)
Insufficient or intermittent sHRT
Caucasian or Oriental
Positive family history
Short stature and small bones
Slim build
Low calcium/Vitamin D intake
Malabsorption
Inactivity
Nulliparity
Smoking
Alcohol
Caffeine
History of secondary causes (Table 2)

TABLE 3

3

PREVENTIVE MEASURES: EXERCISE, CALCIUM, VITAMIN D, OTHER VITAMINS, MINERALS, IRON, TRACE ELEMENTS

It is evident that while bone loss in Osteoporosis can occur rapidly, especially in postmenopausal women, the skeleton is a dynamic living structure and is capable of remarkable healing and remodelling e.g. following fracture in healthy young patients. Therefore, Osteoporosis in later years is not inevitable provided that the skeleton receives the necessary care and attention throughout life.

The following measures to prevent Osteoporosis should be instituted in all patients:

1. EXERCISE AND LIFESTYLE

Peak Bone Mass (PBM) occurs around the age of 18-30 years and exercise probably contributes to this. Even short bursts of physical activity can result in the activation of the bone producing cells of the skeleton, the osteoblasts (Figure 5). The higher the PBM the greater is the skeletal reserve to protect against Osteoporosis in later years.[6,7,8]

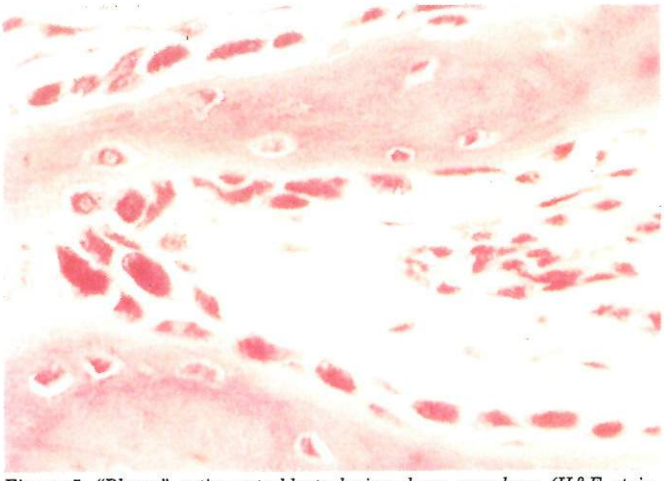

Figure 5. "Plump" active osteoblasts laying down new bone (H&E stain. Reproduced from A Colour Atlas of Bone Disease, V Parsons by kind permission of Wolfe Publishing Limited).

Since both smoking and alcohol impair the formation of normal bone both should be stopped and caffeine avoided since this causes an increased loss of calcium in the urine.[9,10]

It is possible that current data underestimate the Achievable Peak Bone Mass (APBM) since most studies have confined their "normal range" to subjects who have not maximised their bone mass potential. The early institution of vigorous exercise from puberty and avoidance of those factors known to inhibit bone formation will probably provide an enhanced PBM.

In older patients tranquillizers and sleeping tablets should be avoided to decrease the risk of falls. Potential causes of accidents in the home should be minimised and patients should keep warm and physically active. Following fracture and hospitalisation early mobilisation to prevent further bone loss is recommended.

2. CALCIUM AND VITAMIN D INTAKE

Only 30% of the calcium in food is absorbed and low levels may contribute to decreased PBM and in Type II Osteoporosis cortical loss may be due to the progressive decline in absorption with age. It is considered that young women with normal oestrogen levels should take in 1000 mg/day and 1500 mg/day in all postmenopausal women. In adolescence 1500 mg/day is advised during the growth period.

The most convenient source of calcium with low fat intake is skimmed milk and two pints will supply 1440 mg while yoghurt, lowfat, 150G (6oz) contains about 250mg. Other good sources are sardines 50G supplying 250mg of calcium and salmon 50G, 50mg (canned, from the bones), prawns 50G, 80mg, hard cheese 25G, 200mg, cottage cheese 25G, 15mg, bread per slice 30G, 30mg and certain vegetables like brocolli 100G, 80mg, spring cabbage 100G, 30mg, watercress 25G, 50mg, fruit e.g. an orange 50mg, peanuts,

brazil nuts etc. 50G, 40mg and baked beans 100G, 50mg. Although eggs are a source of calcium (and vitamin D), their high cholesterol content is a disadvantage and should be avoided, while the fat content of cheese may not be desirable. Calcium is also available in tablet and effervescent form and may be more convenient and suitable for certain patients whose obesity is a consideration. It also has the advantage of being easily absorbed (biologically available) from the small intestine which may not be the case with certain foods.

Normal vitamin D (which is not a true vitamin but a hormone) levels are essential for calcium absorption and low concentrations in the elderly increase the risk of bone fractures. However, the causes of bone mineral deficiency in patients are various and form an important part of the differential clinical diagnosis during the assessment of any patient with metabolic bone disease.

Sunlight is the best natural source of vitamin D, while oily fish, liver and fortified products including dried milk, yoghurt and breakfast cereals, are easily available. Vitamin D can also be obtained separately in capsule form or as part of multi-vitamin preparations. The total intake should be 400 I.U. per day with blood levels being checked to ensure satisfactory concentrations in the circulation.

3. OTHER VITAMINS, MINERALS, IRON, TRACE ELEMENTS

Patients with inadequate diets of calcium and vitamin D are likely to be deficient in other vitamins e.g. C, A which play a part in collagen formation and other minerals, iron and trace elements. These may be most conveniently provided by taking a multivitamin-mineral preparation containing the Recommended Daily Allowance (RDA) of each.

4 ASSESSMENT OF PATIENT: CLINICAL, CERVICAL SMEAR, MAMMOGRAPHY, PROSTATE, HORMONE PROFILE, BONE DENSITOMETRY, X-RAYS, EXERCISE TOLERANCE

All peri- and postmenopausal women should be screened for Osteoporosis and their suitability for treatment. This will include:

1. Full medical history, clinical examination and measurement of height, weight and arm span. Patients with a history of kidney stones or peptic ulcers (e.g. gastric, duodenal) require careful assessment before introducing added dietary calcium since this may exacerbate these complaints.

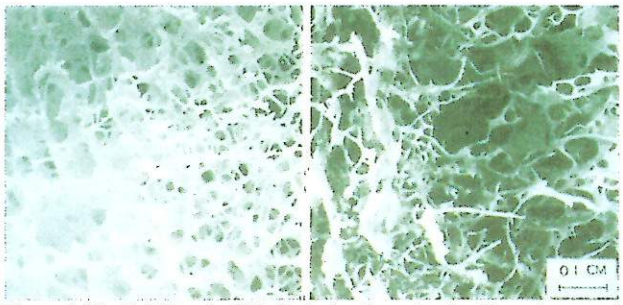

Figure 6. Ward's Triangle: Histological section of neck of femur in normal subject (left) and in Osteoporosis (right) showing extensive loss of trabeculae in untreated patient. (Reproduced by kind permission of Lunar Radiation Corporation).

2. Gynaecological examination to include cervical smear and mammography and urological examination including prostate in men.
3. Hormone profile of pituitary, thyroid, parathyroid, vitamin D, adrenal and ovarian (testicular in men) function with other laboratory tests to exclude anaemia, myeloma, diabetes mellitus, high cholesterol, liver and kidney disease plus 24 hour urine calcium, phosphate, hydroxyproline, hydroxylysine, creatinine clearance, and semen analysis in men.

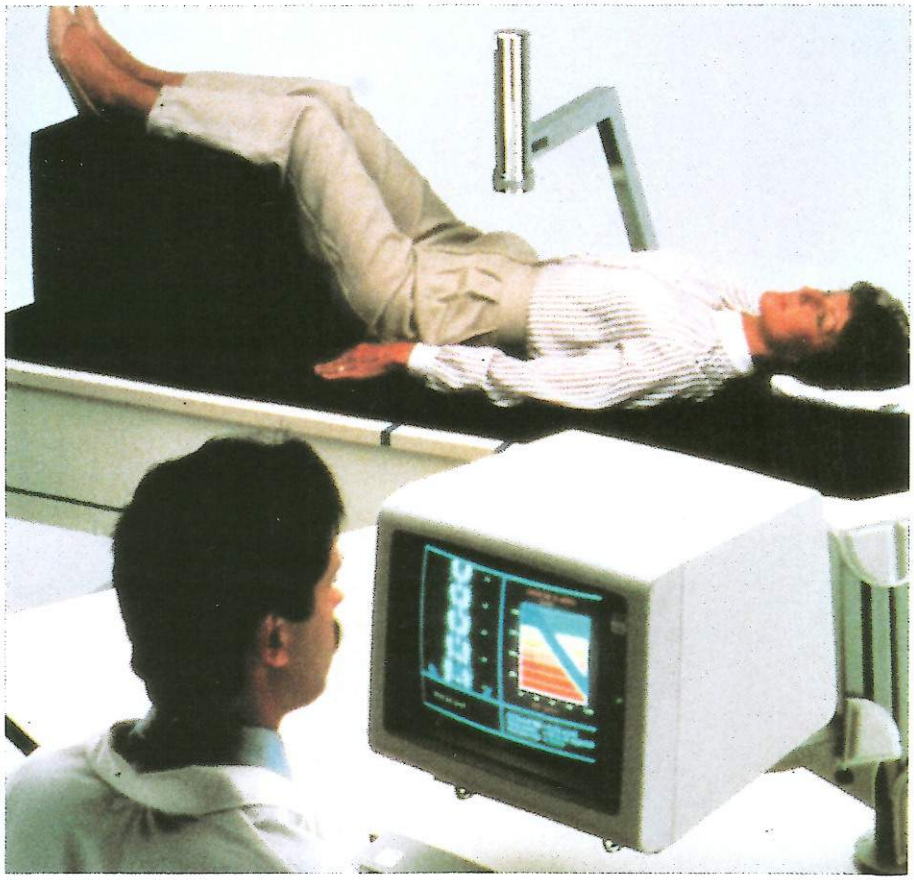

Figure 7. Patient being scanned for Osteoporosis with the Lunar Dual Photon Bone Densitometer. Computer analysis of lumbar spine shown.

4. Dual Photon Bone Densitometry is used to assess the risk of fracture in the spine and both necks of femur, particularly the area of Ward's Triangle which contains almost exclusively trabecular bone and therefore is the point of greatest weakness in Osteoporosis (Figure 6). This computerised method, which is non-invasive, requires no special patient preparation and allows comparison of the patient's bone mineral density (BMD) to be matched for age, weight and ethnic group against normal subjects with healthy bone structure (Figure 7). **While conventional radiology is unable to detect Osteoporosis until there has been a loss of approximately 40% of bone, the Lunar Dual Photon Bone Densitometer can detect changes of only 2-3%.** Although the technique requires only one tenth of the amount of radiation required for a chest X-Ray, the normal precautions concerning pregnancy remain in operation. Typical scans in two of our female patients with Osteoporosis are shown in Figures 8 and 9. Follow-up scans are carried out to assess the individual patient response to treatment.

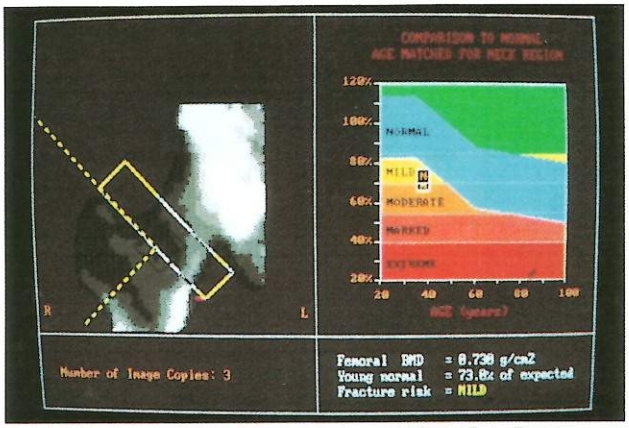

Figure 8. Computer analysis by the Lunar Dual Photon Bone Densitometer of the right neck of femur showing increased risk of fracture with mean loss of 27% of bone. Female patient aged 38 years with irregular periods. (EDC Datafile, reproduced by kind permission of patient).

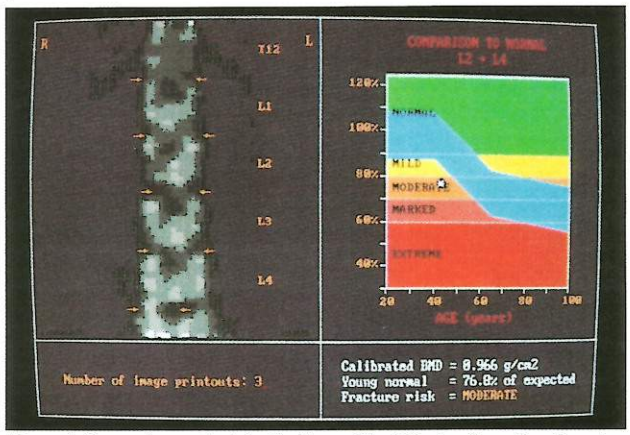

Figure 9. Computer analysis by the Lunar Dual Photon Bone Densitometer of the lumbar spine showing increased risk of fracture with mean loss of 23.2% of bone. Female patient aged 43 years with irregular periods, hot flushes and reduced libido. (EDC Datafile, reproduced by kind permission of patient).

5. X-Rays of the skull, chest, hands, spine, pelvis, long bones and any areas of bone pain to locate fractures together with a resting ECG or further cardiac assessment if indicated.

6. Exercise tolerance requires assessment to determine the patient's existing fitness level and suitability for physiotherapy. Specific exercises, under the close supervision of a Senior Physiotherapist, have been developed to strengthen the muscles of the spine, shoulders, arms, hips, legs and abdominal muscles. In addition to aiding posture and general fitness, the graded traction forces on the bones where the muscles are inserted will produce new bone formation. Patients will be encouraged to proceed with exercise "Bone Builder" programmes and gradual loading to provide the maximum stimulation for skeletal repair.

5 SEX HORMONE REPLACEMENT THERAPY (sHRT): OESTROGEN, PROGESTERONE, TESTOSTERONE

In patients who have had their ovaries removed for medical reasons (oophorectomy), sHRT for many years has been considered essential since the realisation of early Osteoporotic fractures in these women. Premature menopause (below the age of 46 but may present in women under 30 years) is an additional and serious risk factor. Following the menopause the fall in circulating oestrogen and progesterone levels is dramatic returning to pre-pubertal levels although with an adult skeleton, tendons, skin, hair and other tissues to be maintained. To complicate matters further, amongst those with a later menopause there may also exist a group of 'Rapid Bone Losers'.

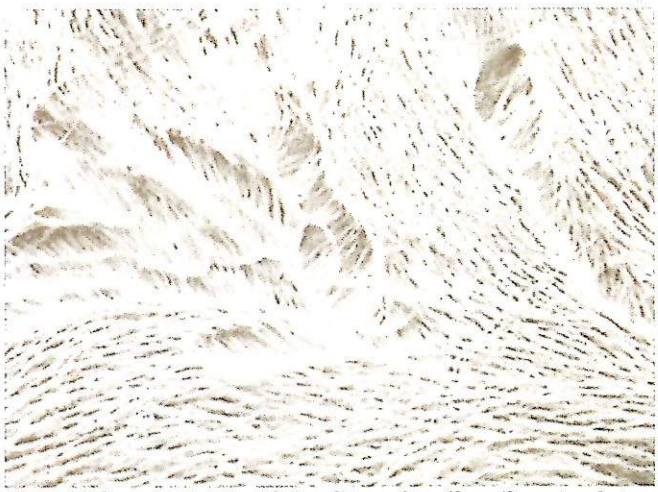

Figure 10. Osteoclast "snail tracks" eroding surface of bone (Scanning electron microscopy. Reproduced from A Colour Atlas of Bone Disease, V Parsons by kind permission of Wolfe Publishing Limited).

Thus, all women over 30 years should be screened to identify those at risk from Osteoporosis so that sHRT can be introduced (and maintained) at the earliest opportunity to prevent further erosion of the skeleton by the osteoclasts (Figure 10).

Formerly there was uncertainty about the long term effects of sHRT but many of these fears were unjustified and have long delayed this important protective treatment for many women. There is now international consensus on the need for oestrogen replacement.[12] Other direct advantages of sHRT on the quality of life include the relief of hot flushes, night sweats, depression, loss of motivation, reduced sex drive, scalp hair loss and are summarised in Table 4.

The latest research on the interaction of sHRT and cancer indicates that it reduces the incidence of malignant disease of the ovaries [13] while the inclusion of the progesterone component allows for regular shedding of the lining of the uterus (endometrium) in those patients who have not had a hysterectomy and may protect against breast cancer.[1] Recent studies also suggest that sHRT may not only protect against Osteoporosis occurring in patients with rheumatoid arthritis but may reduce the risk of developing the condition itself.[14] The effect on ischaemic heart disease is less certain, but oestrogen may be protective.[15]

CONDITIONS IN WHICH BENEFICIAL EFFECTS OF sHRT IN WOMEN HAVE BEEN RECORDED:
Osteoporosis
Vasomotor symptoms (hot flushes)
Depression
Exhaustion
Insomnia
Reduced libido
Vaginal dryness
Brittle nails
Thin skin (loss of collagen)
Loss of scalp hair
Increased facial and body hair
Acne vulgaris (late onset)
Pelvic atrophy
Functional ovarian cysts
Breast and ovarian neoplasms
Rheumatoid arthritis
Cerebrovascular and coronary artery disease (possibly with oestrogen)

TABLE 4

The exact sHRT regimen whether given as tablets, capsules or applied to the skin on adhesive patches for absorption or as implants depends on the individual requirements of the patient.[16,17,18] While oestrogen has been shown to be effective when given alone, it has been suggested that progesterone may have a synergistic effect on bone formation [19] such that the combination has an added advantage as does increased calcium intake.[3] **Recent studies indicate that oestrogen combined with progesterone administered continuously or cyclically may result in an *increase* in BMD by 12-18 months (Figure 11).** Whichever route of administration for sHRT is chosen, it is essential to check that the circulating hormone levels are within an acceptable range.The aim of treatment is to define for an individual patient the Minimum Effective Dose (MED) of sHRT for long term safety to protect and stimulate the skeleton while relieving the symptoms of the Postmenopausal Syndrome (PMS). Since patients may metabolise the same preparations differently, quite apart from variables such as body size and efficiency of absorption, close monitoring should be a routine. This is especially necessary for the conjugated equine "natural" oestrogens extracted from pregnant mares urine and which require metabolism in the liver to unconjugated forms as oestrone and oestradiol–17ß before becoming biologically active (e.g. Prempak C). Ethinyloestradiol however, is only minimally metabolised by the liver so that it is biologically active when given by mouth (e.g. Mercilon). Oestradiol–17ß is different again, since if given orally more than 90% is metabolised in the liver with the products being no longer biologically active. However, with non-oral administration via the skin in patches, biologically active oestradiol–17ß is able to enter the organs and tissues of the body directly (e.g. Estraderm). Progesterone is generally given to ensure regular "periods" as synthetic preparations (e.g. Norgestrel, Norethisterone, Desogestrel, Medroxyprogesterone Acetate) which may need to be varied in certain patients. Women who have had a hysterectomy may be suitable for oestrogen preparations alone although the progesterone component may help to protect against breast cancer.

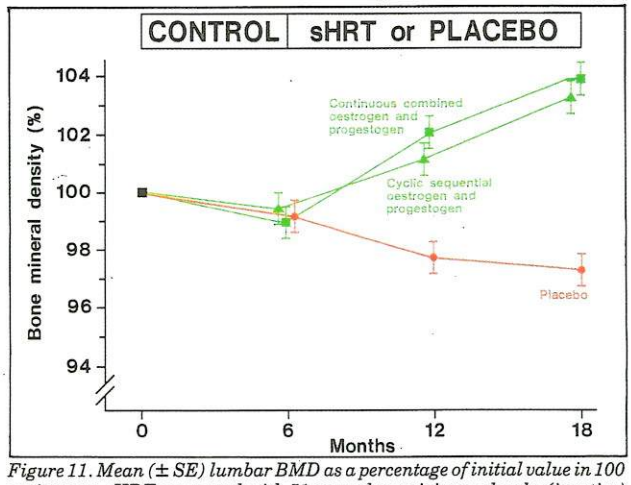

Figure 11. Mean (± SE) lumbar BMD as a percentage of initial value in 100 patients on sHRT compared with 51 controls receiving a placebo (inactive) preparation. (Reproduced from the British Medical Journal by kind permission of the Editor and Authors, Munk-Jensen et al 1988, 196: 1150-1152).

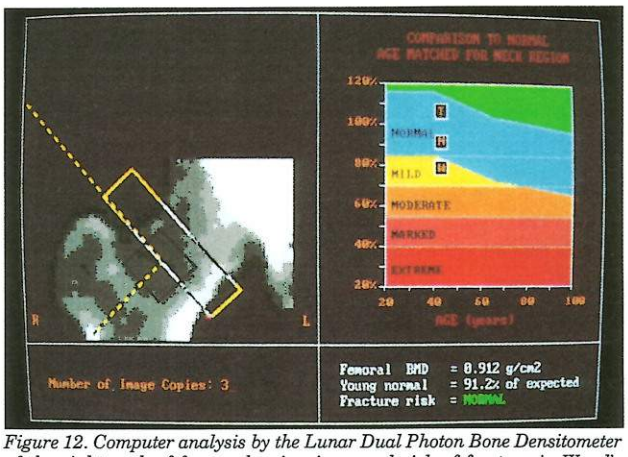

Figure 12. Computer analysis by the Lunar Dual Photon Bone Densitometer of the right neck of femur showing increased risk of fracture in Ward's Triangle (W) with 19% loss of bone but with normal BMD in Greater Trochanter (T) and Neck (N) giving an average bone loss of 8.8%. Male patient aged 43 years with long history of moderate alcohol, caffeine intake and reduced physical activity. (EDC Datafile, reproduced by kind permission of patient).

In general, better hormonal control can be achieved with orally or topically administered preparations than by implants where exceptionally high, non-physiological levels of oestrogen (and testosterone with certain preparations) in the circulation may occur far in excess of the MED required for effective treatment of Osteoporosis or PMS.

Men may require sHRT in the form of testosterone which can be given orally, by intramuscular injection or as implants depending on individual requirements. As in women the circulating levels of testosterone (which is also converted to oestrogen in the body) need to be monitored. Generally testicular function is well preserved in men, often with spermatogenesis and fertility, well into old age thereby protecting the bones from advanced Osteoporosis unless there is a history of alcohol abuse, smoking, caffeine consumption with reduced physical exercise (Figure 12).

The further development of biochemical markers (e.g. osteocalcin) in the blood to provide measurable evidence of new bone formation and the activity of the Osteoporotic process together with Dual Photon Bone Densitometry to record bone mass may overcome the problems of defining the MED of sHRT for maximum efficacy with the minimum of side effects in patients who may be on treatment for 40 years or more.

6 OTHER THERAPY: CALCITONIN, FLUORIDE, DIPHOSPHONATES, THIAZIDES, ANABOLIC STEROIDS

Calcitonin is a naturally occurring hormone secreted from the parafollicular (or C cells) of the thyroid gland which together with parathyroid hormone (PTH from the four parathyroid glands behind the thyroid gland) regulates calcium levels in the body. Preliminary studies suggest that if given by injection [20] or intranasally, [21] calcitonin may slow the progress of Osteoporosis while the presence of oestrogen and androgens may be required to facilitate its action.[22] The value of fluoride, diphosphonates, thiazides and anabolic steroids is less certain and should be avoided until further clinical data are available.

7 CONCLUSION

Osteoporosis in the United Kingdom is now reaching epidemic proportions with a female population over 45 years of age numbering in excess of 9.6 millions all of whom are at risk. Yet with DUAL PHOTON BONE DENSITOMETRY SCREENING for early detection and the correct treatment, it can be arrested with the relief of much unnecessary pain to the patient, the prevention of severe disability and death. THIS CAN BE DONE NOW. For the future the most challenging aspects of our research at EDC will be the restoration of the osteoporotic skeleton in the affected patient to normal.

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