I should like to thank Professor Barbagallo-Sangiorgi for inviting me to speak again on a topic I discussed here some years ago. During this time our knowledge of the pathophysiology of post-menopausal osteoporosis has advanced consistently and several therapeutic trials have been undertaken. The main scheme I proposed then has not changed substantially; nevertheless at present it must be integrated with more recent results, particularly those in the field of vitamin D metabolites and I shall communicate now the status of the art.

Post-menopausal osteoporosis is a very common pathological condition characterized by a reduction in bone mass that is mainly the result of bone resorption. A spongy appearance of cortical bone is observed as a consequence of the presence of large resorption lacunae, and a thinning of the trabeculae of cancellous bone may also be apparent. No osteoid seams are present, which are characteristic of osteomalacia. Thus bone mass is reduced but the mineralisation of the remaining bone is normal.

The skeletal changes, that are mostly evident in spine, lead to a progressive brittleness of bones with increased liability to fractures; the painful crush fractures of vertebrae lead to kyphotic deformity of the spine and reduction in stature.

It has been largely demonstrated that oophorectomy and menopause accelerate bone loss in women. Estrogen lack leads to a negative calcium balance with a secondary increase in bone resorption for homeostatic purposes. Estrogen therapy decreases significantly bone resorption with a positive transformation of calcium balance.
In 1963 we demonstrated an impairment of intestinal radio-
calcium transport in post-menopausal osteoporosis;\textsuperscript{6} this observa-
tion has been largely confirmed thereafter.\textsuperscript{7,14} Subsequently we
demonstrated that the impaired intestinal calcium transport returned
to normal after a 6 month treatment with an oestrogen-gestogen
combination;\textsuperscript{15} these results have been recently confirmed.\textsuperscript{16}
The possibility that estrogen lack might be responsible for the
impaired absorption of calcium with secondary loss of bone was then
considered and the positive therapeutic effect of estrogens on post-
menopausal osteoporosis did find its rationale.

VITAMIN D METABOLITES

It is widely known that vitamin D has not a direct action on
its targets. Cholecalciferol, that is the vitamin D\textsubscript{3} synthesized
by the skin and largely dependent on exposure to ultraviolet light,
is converted in the liver to 25 hydroxyvitamin D\textsubscript{3} (25OH vitamin D)
which in turn must be converted in the kidney to 1.25 dihydroxy-
vitamin D\textsubscript{3} (25(OH)\textsubscript{2} vitamin D) the most effective and rapidly acting
of the vitamin D metabolites.\textsuperscript{17} 1,25(OH)\textsubscript{2} vitamin D promotes the
active transport of calcium in the gut; its plasma level is
dependent upon the calcium needs of the organism; particularly
1,25(OH)\textsubscript{2} vitamin D is actively synthesized in hypocalcemic
conditions due to nutritional calcium defects, with a consequent
adaptation of the intestinal calcium transport.\textsuperscript{17}

In post-menopausal osteoporosis the serum level of 1,25(OH)\textsubscript{2}
vitamin D is lower than in normal age-matched controls,\textsuperscript{18,20}
whereas the vitamin D status measured by the serum 25OH vitamin D
level appears to be excellent: the levels of 25OH vitamin D are
not only higher than in age-matched non-osteoporotic controls but
higher than in young normal women as well.\textsuperscript{19} This could be
accounted for by an increased activity of liver 25-hydroxylase
through an inadequate product-inhibition of this enzyme.

Similarly the increased serum levels of 24,25(OH)\textsubscript{2} vitamin D
in our post-menopausal osteoporotic women support this hypothesis:\textsuperscript{20}
it is largely known that there is a reciprocal relationship of
1,25(OH)\textsubscript{2} vitamin D and 24,25(OH)\textsubscript{2} vitamin D in the sense that under
circumstances that stimulate the production of 1,25(OH)\textsubscript{2} vitamin D
there is a repression of the ability to produce 24,25(OH)\textsubscript{2} vitamin
D and vice versa.\textsuperscript{21}

Every physician knows that vitamin D given as such is
ineffective in the treatment of post-menopausal osteoporosis. On
the other hand post-menopausal osteoporotic women given 1 microgram
of 1,25(OH)\textsubscript{2} vitamin D\textsuperscript{3} daily, that is the physiological dose,
showed within 10 days a dramatic improvement of the intestinal
transport of radiocalcium.\textsuperscript{22} A similar treatment with 24,25(OH)\textsubscript{2}