Introduction for the Symposia Entitled:

Newly Discovered Actions of 1,25-Dihydroxyvitamin D_3 and Osteoporosis: Basis and Treatment (42910)

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Vitamin D was originally discovered because the bone disease rickets was found in epidemic proportions in Northern Europe, North America, and Northern Asia at about the time the concept of the vitamins made its appearance (about 1900–1920). Sir Edward Mellanby, in reacting to the discovery of the fat-soluble vitamin A and water-soluble vitamin B by McCollum and co-workers at Wisconsin (1, 2) and Mendel and Osborne at the Connecticut Experiment Station (3), conceived that rickets might also be a nutritional disorder. By feeding dogs a diet of oatmeal and maintaining them indoors, he produced the same disease rickets prevalent in the human population (4). Because he was able to cure the disease with cod liver oil that was shown to contain fat-soluble vitamin A, Sir Edward Mellanby considered this curing of the bony disease rickets as another property of fat-soluble vitamin A. However, McCollum and co-workers then at Johns Hopkins demonstrated clearly the existence of the new antirachitic factor which he termed Vitamin D (5). In concomitant discoveries, Huldshinsky (6) found that rickets could also be cured by ultraviolet irradiation, and Steenbock (7) demonstrated that ultraviolet irradiation of not only skin but also food produced the antirachitic vitamin D. Vitamin D, therefore, produced by the irradiation of skin or by consuming vitamin D-rich oil such as cod liver oil then became known as a substance required for the mineralization of the skeleton. Over the next several decades the structure of the vitamin D compounds became known and the general physiology of vitamin D action was established (8). Thus, vitamin D stimulates the intestine to absorb calcium and secondarily phosphorus. It was also found to be responsible for the mobilization of calcium from bone (9), and more recently was found to stimulate renal reabsorption of calcium (10). The elevation of plasma calcium and phosphorus, as a result of vitamin D administration, then resulted in the mineralization of the skeleton (11). These functions of vitamin D in the intestine, bone, and kidney became known as the classical actions of vitamin D. However, it is clear that vitamin D plays other important roles in bone such as stimulation of the remodeling system in adults, which is first a resorption of bone followed by formation (12). Thus, the classical actions of vitamin D began to be expanded.

During the 1960 era, it became known that vitamin D must be metabolically altered before it could function in these classical actions, leading ultimately to the discovery of the vitamin D endocrine system and its active hormone, 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) (8). Shortly thereafter came the discovery that 1,25-$(OH)_2D_3$ interacts with a nuclear receptor and that its mechanism of action is very closely related to the classical steroid hormone mechanism of action (8, 13). Nuclear localization of this active hormonal form of vitamin D was noted specifically in not only the target tissues resulting in the classical actions of vitamin D but also in the nontarget tissues not previously appreciated as target organs (14). For example, specific nuclear localization was found in the parathyroid gland cells (15), in the islet cells of the pancreas (16), in the sertoli cells of the reproductive organs (17), in placenta (18), in endocrine cells of the stomach (14), and in certain cells of brain (19). The discovery of the receptor for 1,25-$(OH)_2D_3$ was followed by its demonstration in a wide variety of tissues very much like the nuclear localization studies (20). Thus, receptors for 1,25-$(OH)_2D_3$ were found in a long list of what was previously not suspected as being a target organ of vitamin D.

With the availability of synthetic amounts of 1,25-$(OH)_2D_3$ in labeled and unlabeled forms have come cell biology studies in which it can be demonstrated that

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the vitamin D hormone can cause differentiation of a variety of cell types (21–24), is found necessary for certain aspects of reproduction (25, 26), and is involved in the immune system (27). Furthermore, the presence of the receptor in a large number of cancer cell lines and in solid tumors has led to experiments in which vitamin D compounds may be used in the treatment of malignancy (28). Our vision then of vitamin D must be expanded beyond the classical actions and one symposium organized herein is devoted to a brief review of some of these nonclassical functions of vitamin D.

With the availability of the calciotropic hormones, namely, 1,25-$(OH)_2D_3$, human parathyroid hormone, and calcitonins, has come the possibility that knowledgeable use of these compounds could be instrumental in controlling metabolic bone disease. In fact, these agents have been applied to a number of metabolic bone diseases with considerable success. Thus, the active form of vitamin D can be used for the treatment of hypoparathyroidism, for the suppression of secondary hyperparathyroidism of renal osteodystrophy, and the treatment of vitamin D-resistant rickets, and calcitonin can be used to suppress bone pain and to prevent bone resorption. Human parathyroid hormone has been championed as a possible stimulator of the bone remodeling system.

The most widespread of all of the metabolic bone diseases is osteoporosis, a disease whereby the bone mass is diminished to a point where fracture of the skeleton results either spontaneously or with minor trauma. Prevention of loss of skeletal mass or the rebuilding of skeletal mass becomes the primary approach in the treatment of this widespread disease. Besides the calciotropic hormones, other approaches to the management, treatment, and prevention of osteoporosis have come forth. The second symposium then is devoted to providing recent information on the extent, diagnosis, and treatment of osteoporosis. As will be evidenced from the presentations, we will expect major advances in our management of this widespread bone disease.

To present these symposia, workers in the forefront of each phase have been selected. The following will present a write-up by the authors who presented these symposia at the 1988 FASEB meeting in Las Vegas. In a sense, these symposia are introductions in themselves because we believe that in the next 10 years, masses of new information will become available in each of the areas discussed.

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