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Ed. Note - This overview was originally presented at the International Symposium on Clinical Disorders of Bone and Mineral Metabolism, May 9-13, 1983. The following list indicates the presentations given in this session at the Symposium and the contents of the corresponding chapter in the Proceedings of the Symposium published by Excerpta Medica. The numbers in parentheses refer to pages in this volume. Complete information about the contents of the Proceedings can be found at the back of this issue.

Vitamin D metabolities: New physiologic and clinical insights. M.R. Haussler, S. Dokoh, D.J. Mangelsdorf, C.A. Donaldson, and J.W. Pike (68)

Vitamin D metabolism in man: Contributions from clinical studies. S.W. Stanbury and E.B. Mawer (72)

The cardinal role of 1,25-dihydroxyvitamin D_3 in mineral homeostasis. H.F. DeLuca (78)

The role of $1,25(OH)_2D_3$ in the pathogenesis of osteomalacia. H. Rasmussen (82)

With the availability of stereospecific assays for vitamin D and its metabolites, many clinicians now measure these sterols in evaluating the pathogenesis and treatment of diseases affecting mineral and skeletal homeostasis. Since some of these assays are commercially available, it seems appropriate to reflect on what they measure and how to interpret the results. Much new information published over the past 10-12 years can be confusing. Other sections of this Symposium dealt specifically with certain diseases affecting vitamin D metabolism, but Haussler, Stanbury, DeLuca, and Rasmussen dealt directly with the biological relevance of sterol production, quantitation, and the interpretation of the sterol assay data in light of the presumed activities of the vitamin's metabolites.

As indicated by Haussler and colleagues (pp. 68 ff.), the competitive protein binding assays (CPBA) have had the greatest usage, but we must be aware of the improved technology suggested by the novel cytoreceptor assay (1), polyclonal radioimmunoassay (RIA) (2), monoclonal RIA (3), and innovative, facile preparative approaches to CPBA (4). Continuing progress in the development of selective, sensitive, precise, convenient assays seems likely. Although available, quantitation of the vitamin D carrier protein (DBP) has not gained wide usage in the interpretation of "bound" or "free" sterol (5). If the role of DBP in blood sterol transport is indeed passive and not one of carrier-mediation into tissues, it seems likely that estimates of "free" sterol could be useful in situations in which sterol transport is either compromised or augmented by changes in the protein's concentration and/or its occupancy by sterols.

Two controversial areas in the interpretation of sterol values are the role(s) of sterols other than 1,25-$(OH)_2D$ and the relevance of the extrarenal production of 1,25-$(OH)_2D$. These areas were directly addressed in this section. The emphasis of Stanbury and Mawer (pp. 72 ff.) on 1,25-$(OH)_2D$ underscored the view that this sterol is the cardinal metabolite in the expression of the vitamin's "traditional" biological activity. The clear-cut alliances of several relevant diseases with 1,25-$(OH)_2D$ underproduction, overproduction, and resistance support this position. Extrarenal 1,25-$(OH)_2D$ synthesis currently appears to be clinically significant in sarcoidosis and certainly of interest in pregnancy, but as DeLuca (pp. 78 ff.) indicated, of uncertain in vivo significance in other tissues.

Rasmussen (pp. 82 ff.) provided a broad view of sterol action and addressed the controversial areas dealing with the role of other sterols in mineral and skeletal homeosta-

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tis. In contrast to Rasmussen's contention, DeLuca indicated that the introduction of a fluoro group at position C-25 markedly reduced biological activity, but that a fluoro group at C-24 did not reduce biological effects.

The concept of both renal and extrarenal biosynthesis of 1,25-$(OH)_2D$ has withstood challenges far better than hypotheses of new target tissues for this potent sterol. Many reports have convincingly demonstrated the presence of high affinity, selective 1,25-$(OH)_2D$ receptors in tissues not usually associated with major translocations of mineral ions (6). This latter review also suggested a role for 24,25-$(OH)_2D$ in various activities, but Haussler and co-workers revealed their present inability to confirm these findings. An exciting development by Pike (7) is the production of monoclonal antibodies to the 1,25-$(OH)_2D$ receptor, which provides a new probe to reveal the topography and relevance of the sterol-receptor association. The influence of 1,25-$(OH)_2D$ on cellular differentiation, whether calcium-mediated or not, will clearly attract future investigators.

The influences of 1,25-$(OH)_2D$ on cellular differentiation provide some basis to broaden our viewpoints about the action(s) and target tissues for vitamin D. This area, in relationship to myelogenous leukemia cells, has recently been reviewed (8). Further work may be expected in the delineation of sterol effects on cells not classically associated with bulk transfer of minerals.

Interesting clinical observations by Stanbury and Mawer suggested the importance of several factors in carefully interpreting sterol assay values. Nutritional or photobiological, hormonal, and possibly ionic and autoregulatory influences can condition blood sterol concentration. Recent studies of the clearance of sterol(s) from blood suggest that alterations in sterol degradation might characterize certain conditions, such as the augmented loss of water-soluble sterol conjugates into the urine of patients with cholestatic liver disease (9).

The relationships among 1,25-$(OH)_2D$ and substrate sterol, ions, and hormones addressed by Stanbury and Mawer underscored their importance in the interpretation of single and perturbed plasma 1,25-$(OH)_2D$ levels. Provocative testing of 25-OHD-1α-hydroxylase activity will clearly be an active area for future workers (10).

A major clinical focus for the controversy surrounding the importance of 1,25-$(OH)_2D$ is the observation that osteomalacia can develop in the presence of slightly high, normal, or low blood concentrations of this sterol. Several factors are relevant: substrate (25-OHD) availability, dietary mineral content, age of the patient or rate of growth, degree of secondary hyperparathyroidism, renal function. In other words, normal 1,25-$(OH)_2D$ blood levels may be inappropriately low in a situation demanding very high levels in order to provide sufficient intestinal mineral transport for mineralization of the skeleton. The observation that 1,25-$(OH)_2D$ blood levels are five to six times higher during the healing of vitamin D-deficient osteomalacia suggests the possibility of a non-PTH, 1α-hydroxylase-stimulator of skeletal origin.

References

1. Mangolas S, Culler F, Howard J, Brickman A, Deftos L. J Clin Endo & Metabol 1983;56:751.
2. Clemens T, Hendy G, Papapoulos S, Fraher L, Care A, O'Riordan J. Clin Endocrinol (Oxford) 1979;11:225.
3. Perry H, Chappel J, Clevinger B, Haddad J, Teitelbaum S. Program of 5th ASBMR Meeting, San Antonio, Texas, 1983, p. A65.
4. Reinhardt T, Horst R, Orf J, Hollis B. Program of 5th ASBMR meeting, San Antonio, Texas, 1983, p. A66.
5. Bouillon R, Van Assche F, Van Baelen H, Heyns W, DeMoor P. J Clin Invest 1981;57:589.
6. Norman A, Roth J, Orci L. Endocrine Reviews 1982;3:331.
7. Pike J, Donaldson C, Marion S, Haussler M. Proc Nat Acad Sci 1982;79:7719.
8. Koeffler HP. Blood 1983;62:709.
9. Jung R, Davie M, Siklos P, Chalmers T, Hunter J, Lawson D. Gut 1979;20:840.
10. Prince R, Wark J, Omond S, Opie J, Eagle M, Eisman J. Clin Endocrinol 1983;18:127.