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On the Nature of the Toxic Action of Vitamin D.

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Early experience with incompletely purified preparations of vitamin D demonstrated a high degree of toxicity which was first ascribed to by-products such as toxisterol and tachysterol. Later calciferol also was found to be toxic in large doses. While hypercalcemia commonly occurs with intoxication from calciferol, viosterol, toxisterol or tachysterol, it has been amply demonstrated that hypercalcemia is not *per se* the cause of toxicity.

The fact that the symptom complex of intoxication is identical, qualitatively, when produced by any of these agents leads to a tentative assumption that intoxication in each case may not be due fundamentally, to hypervitaminosis D, but to the formation of toxic products either in the alimentary canal or in the process of intrinsic metabolism when an excess of the vitamin in the form of calciferol or viosterol has been administered.

Crystalline ergosterol dissolved in ether was irradiated with a quartz mercury vapor lamp, according to directions kindly supplied by Dr. F. G. McDonald. One lot assayed by the line test yielded 9,000,000 (±15%) units per gram of original ergosterol. A part of this was recovered from the ether without purification; consequently the material comprised a mixture of calciferol, ergosterol and other products in unknown proportions.

A portion of this material was then further irradiated and on recovery without purification yielded, on assay, 3,000,000 (±15%) units of vitamin D per gram of original ergosterol, showing that there had been further decomposition so that there must have been still a larger proportion of other products and less unchanged ergosterol (Gp II).

Next, a solution of calciferol in oil, 1,000,000 units per gram of solution, was allowed to stand open in a warm room until it became cloudy and the quality of taste was markedly altered. On assay this was found to contain only 50,000 units per gram (Gp III). In Table I are shown the results of experiments on dogs with these preparations.

Group I comprised 12 male dogs of comparable age, weight and physical condition. These were given daily by mouth 12,000 vitamin D units of the first preparation per kilo of body weight. Of

TABLE I.

Group	No. dogs	Vitamin D I.U./kg/day	No. toxic in 15 days	Assay of preparation. Units per g of original ergosterol
I	12	12,000	7	9,000,000 (±15%)
II	14	4,000	11	3,000,000 (±15%)
III	13	800	9	*
IV	14	20,000	0	†

*Viosterol (1,000,000 units per gram, 16,000,000 units per gram of original ergosterol). Allowed to decompose until assayed at 50,000 units per gram.

†Viosterol (1,000,000 units per gram). Stock solution prepared from material practically free from toxisterol, but containing a small amount of unchanged ergosterol.

these, 7 showed definite evidences of intoxication in 15 days, when the experiment was discontinued.

Group II comprised 11 male and 3 female dogs, comparable to those in Group I. These were fed daily 4,000 units of vitamin D per kilo in the form of the second preparation, which had been overirradiated. Of these, 9 males and 2 females were intoxicated in 15 days.

Group III consisted of 8 males and 5 females. These were fed daily of the decomposed material an amount sufficient to make up 800 vitamin D units per kilo. Of these, 3 females and 6 males became toxic in 15 days.

Group IV. Of 14 dogs receiving daily 20,000 units of vitamin D per kilo in the form of viosterol (1,000,000 units per gram), none showed any symptoms of intoxication within 15 days, yet they received the largest dose in vitamin D units.

These experiments strongly suggest that the degradation products were responsible for the intoxication. It is possible that the intoxication resulting from doses of calciferol above 20,000 units per kilo per day may be due to formation of similar compounds when the organism is overloaded with the vitamin.