

S., *Cancer Chemotherapy Rep.*, 1962, v20, 57.

5. Grobstein, C., *J. Exp. Zool.*, 1953, v124, 383.

6. Dawe, C. J., *Nat. Cancer Inst. Monogr.*, No. 11, 1963, 222.

7. Dawe, C. J., Shaw, M. G., Morgan, W. D., *Fed. Proc.*, 1963, v22, 605.

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Cyst Formation in the Parathyroids and Muscular Dystrophy Induced by Dihydrotachysterol and Calcium Acetate.* (29186)

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The formation of cavities in the parathyroids has frequently been noted as an accidental finding in man and other vertebrates. Its many variants have been described under such names as "cystic degeneration," "colloid formation," "follicular transformation," "vesicle formation," etc. On purely theoretic grounds, this change has been variously ascribed to degeneration, increased secretion, hormone storage, invasion of thyroid tissue into the parathyroid, or malformation of the bronchial-cleft system(1-3). However, the causative factors could not be analyzed experimentally since it has never been possible to reproduce this singular lesion by any type of intervention. There is a voluminous literature on induction of simple parathyroid hypertrophy, hyperplasia or atrophy by variations in dietary intake of calcium, phosphorus and vitamin-D compounds(4-11), but no studies have apparently been made on the morphology of the parathyroids following simultaneous overdosage with vitamin-D derivatives and calcium compounds. It was of some interest, therefore, when recently we observed, during experiments on calciphylaxis, that rats concurrently treated with dihydrotachysterol (DHT) and calcium acetate regularly develop cystic parathyroids and a singular form of muscular dystrophy.

Experimental. Forty female Sprague-Dawley rats of the Holtzman strain, with a mean initial body weight of 98 g (range 95-103 g) were subdivided into 4 equal groups: Group

1 acted as untreated controls. Group 2 received 30 μ g of dihydrotachysterol "DHT" (Dr. A. Wander S. A., Bern, Switzerland) in 0.5 ml corn oil by stomach tube, once daily. Group 3 was given 1 mM of calcium acetate in 2 ml of water, also by stomach tube, twice daily. Group 4 received both DHT and calcium acetate as Groups 2 and 3 respectively.

The animals were kept exclusively on Purina Lab Chow (Purina Co. of Canada) and tap water. The experiment was terminated on the sixteenth day by killing the survivors with chloroform. Specimens of the thyroparathyroid apparatus and of the quadriceps muscle were fixed in alcohol-formol (1 part of 10% neutral formalin, 4 parts of 80% alcohol) for subsequent embedding in paraffin and staining with von Kóssa and PAS techniques.

Results. No mortality or clinical evidence of motor impairment occurred among the animals of the first 3 groups, but by the tenth day those given DHT + calcium acetate began to exhibit signs of muscular weakness as judged by their hesitating gait. Subsequently, mortality began and 80% of the animals were lost in this group by the sixteenth day when the experiment was terminated. At autopsy, all the rats of Group 4 which succumbed, as well as those that were killed at the end of the experiment, exhibited slightly enlarged parathyroids and widespread, light patches throughout the skeletal musculature. No such anatomic changes were observed in any of the other groups. Combined treatment with DHT + calcium acetate also led to severe cardiac and renal calcification but minor degrees of the same

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changes were also noted among the rats given DHT alone.

Histologic examination of the parathyroid tissue showed no detectable change in the

animals of the first 3 groups, while in all those given DHT + calcium acetate, it assumed a spongy aspect, being studded with cystic cavities of different size and shape.

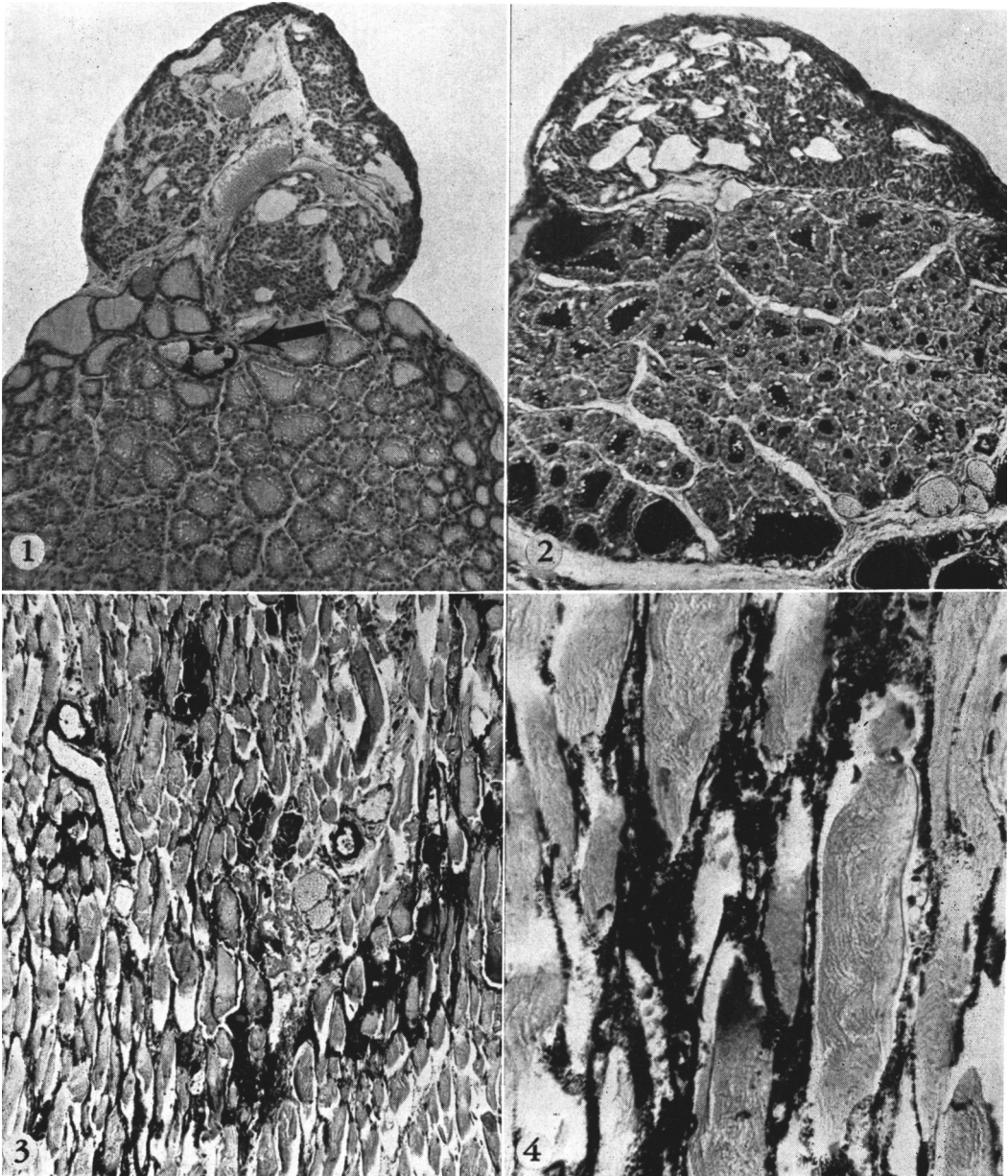


FIG. 1. Polycystic parathyroid with calcification (arrow) in parathyroid artery (von Kóssa, $\times 120$).

FIG. 2. Unlike in the adjacent thyroid follicles, there is no PAS-tingible fluid in the cavities of the polycystic parathyroid (PAS, $\times 120$).

FIG. 3. Quadriceps with extensive calcification of arteries and sarcolemma sheath. Muscle fibers themselves are only occasionally calcified (von Kóssa, $\times 120$).

FIG. 4. Higher magnification of a region from Fig. 3. Here, the sharp localization of calcification to the sarcolemma sheath is even more evident (von Kóssa, $\times 460$).

The lumens of these cysts were filled with a mildly basophilic precipitate which was much less dense than the adjacent thyroid colloid and, unlike in the latter, gave no PAS reaction. Occasionally, disintegrating cells could be seen within the cyst cavities, but usually most of the contents were lost during manipulation for staining (Fig. 1, 2). The skeletal musculature of this group showed widespread patches of degeneration with moderate calcium deposition, especially around the sarcolemma sheath, and intense Mönckeberg type of calcification in the muscular arteries (Fig. 3, 4).

Discussion. It appears that combined treatment with DHT and calcium acetate causes a highly specific change in the parathyroids which is primarily characterized by cyst formation. The functional significance of this lesion is not clear but it is tempting to assume, as a working hypothesis, that our treatment somehow interfered with the release of parathyroid secretion and that the newly formed cavities represent "retention cysts." This parathyroid response is associated with widespread functional and structural derangements in the skeletal musculature. The observation is reported in the hope that a technique permitting consistent production of such parathyroid cysts may be useful in studying the factors that regulate parathyroid function and in clarifying the effect of

these glands upon the skeletal musculature in conditions other than parathyroprival tetany.

Summary. Experiments on rats indicate that oral administration of dihydrotachysterol (DHT) plus calcium acetate, regularly induces extensive cyst formation in the parathyroids, associated with widespread degenerative changes in the skeletal musculature. Under the conditions of these experiments, neither DHT nor calcium acetate alone produced such changes.

1. Bargmann, W., in *Handbuch der Mikroskopischen Anatomie des Menschen*, Wilhelm v. Möllendorff, Ed., Springer, Berlin, 1939, v6, part II, p137.
2. Herxheimer, G., in *Handbuch der speziellen pathologischen Anatomie und Histologie*, Henke & Lubarsch, Ed., Springer, Berlin, 1926, v8, p548.
3. Gilmour, J. R., *J. Path. Bact.*, 1939, v48, p187.
4. Hanssler, H., *Z. gesamt. exp. Med.*, 1954, v123, p91.
5. Engfeldt, B., Hjertquist, S. O., Strandh, J. R. E., *Acta Endocrinol.*, 1954, v15, p119.
6. Stoerk, H. C., Carnes, W. H., *J. Nutrition*, 1945, v29, p43.
7. Sinclair, J. G., *Anat. Rec.*, 1941, v80, p479.
8. Bastenie, P., Zylberszac, S., Dustin, A. P., *Comp. rend. Soc. Biol.*, 1939, v132, p95.
9. Pierre, M., De Boissezon, P., Lombard, C., *idem.*, 1939, v130, p341.
10. Sinclair, J. G., *J. Nutrition*, 1942, v23, p141.
11. Hanssler, H., *Klin. Wchnschr.*, 1954, v32, p137.

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The Absence of Anticonvulsant Properties of Quinacrine and Chloroquine in Mice.* (29187)

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Méndez and Hartley(1) reported the disappearance of petit mal seizures in a patient receiving quinacrine for a *Giardia lamblia* intestinal infestation. Since then, there have been several reports concerning the efficacy of quinacrine and/or chloroquine in the treatment of petit mal refractory to other drugs

(2,3,4,5,6,7,8,9). In view of these reports, it seemed of interest to compare these compounds with phenobarbital and trimethadione as to their efficacy in modifying seizures produced in mice by electroshock and pentylene-tetrazol (Metrazol).

Materials and methods. Adult male albino mice obtained from the Arthur Sutter Farms (Rockland strain), weighing 20 to 25 g were

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