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Production in Guinea Pigs of Fibrous Bone Lesions with Parathyroid Extract.

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Askanazy[1] found a parathyroid adenoma in a case of *ostitis fibrosa* and he suggested a cause and effect relationship between the parathyroid tumor and the bone disease. After his finding, many other instances of parathyroid enlargement were reported in association with *ostitis fibrosa deformans, ostitis fibrosa cystica,* osteomalacia and rickets. Parathyroid enlargement has also been noted in rats suffering from experimental rickets. The consensus until recently was that the parathyroid enlargement observed in association with these bone diseases was of a secondary nature, and appeared as a result of a compensatory hypertrophy due to the bone deficiency.

Mandl,[2] and after him others, removed parathyroid adenomas in cases of *ostitis fibrosa cystica* and reported rapid clinical improvement of their patients, with cessation of the negative mineral balance.

We felt that, if the extirpation of a parathyroid adenoma resulted in the clinical improvement of a case of *ostitis fibrosa cystica,* injections of parathyroid extract might produce similar or analogous bone lesions, if parathyroid hypersecretion was at the basis of the disease.

Attempts have been made to produce experimental *ostitis fibrosa* by dietary deficiencies and by injury to the bone marrow[3, 4] with negative results.

Dogs treated with parathyroid extract develop very extensive bone resorption, in both the cortex and the medulla, but fibrous repair is difficult to elicit. It is suggestive that in the dog doses large enough to raise serum calcium to very high levels and to produce a recognizable overdosage complex, sometimes leading to death, are not sufficient to cause lesions severe enough to elicit the response of fibrous repair. In the guinea pig, however, doses which, while high in terms of parathormone units, produce very much smaller effects on serum calcium and few, if any, of the overdosage effects, will cause bone lesions with fibrous repair. The reason is probably to be

[1] Askanazy, M., *Arb. a. d. Path. Anat. Inst. Tübingen,* 1904, iv, 398.

[2] Mandl, F., *Arch. f. klin. Chir.,* 1926, xcliii, 1, 245.

[3] Dibbelt, W., *Verhandl. d. deutsch. path. Gesell.,* 1909, xxxiii, 13.

[4] Nissen, R., *Deutsche Z. f. Chir.,* 1925, cxci, 197.

sought in the metabolic differences between the dog and guinea pig, and their differing metabolic responses to parathormone injection. The incidence in man of fibrous dystrophies associated with hyperparathyroidism is probably to be explained by associated or independent metabolic derangements.

In previous attempts to produce *ostitis fibrosa* experimentally, the animals were sometimes kept on deficient diets, as stated above. In our experiments, the guinea pigs were on their normal diet of carrots, cabbage, hay and oats, and most of them gained weight. Sixty-three experimental animals were studied, and fully the same number of controls were also examined.

In the guinea pig we have regularly produced with subcutaneous injections of parathormone the bone changes which satisfy all the criteria of *ostitis fibrosa,* including the appearance of new bone (osteoid). The latter appears as soon as the reparative processes are permitted to operate with sufficient intensity. A guinea pig permitted to go for a few days without parathormone, after previous parathormone treatment, shows an abundance of osteoid tissue beneath the periosteum and endosteum, in the haversian canals, and in fibrous tissue in the metaphysis just distal to the epiphyseal cartilage plate. In passing, we wish to state that the osteoid tissue results not from the metaplasia of the connective tissue, but from rejuvenated osteoblasts present in the scar tissue.

It was of course necessary to use relatively large doses of parathormone to produce fibrous changes in the bones of guinea pigs, compared with the amounts necessary to induce bone resorption in the dog. The resistance of the guinea pig to parathormone has been pointed out,[5] and this resistance is probably attributable to the effect of the exogenous metabolism of the guinea pig, shown by the alkaline urine when fed their normal diet.

We produced bone changes in guinea pigs with as little as 10 units of parathormone, and with 20 to 30 units daily for 3 weeks we obtained very extensive resorption and fibrosis of the bones. Even one dose of 60 units given to a 300 gm. guinea pig produces extensive resorption of the bone, cessation of bone formation and infraction of the cortex in 48 hours. Such guinea pigs may die, with extensive bone destruction, if the large doses are continued. The bone changes described were observed in all the long bones and in the ribs.

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[5] Bodansky, A., Blair, J. E., and Jaffe, H. L., PROC. SOC. EXP. BIOL. AND MED., 1930, xxvii, 708.

generous cooperation in supplying most of the parathormone used in these experiments.

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The Nerve Pathways in the Vomiting of Peritonitis.

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A careful review of the literature has failed to disclose any explanation of the mechanism of vomiting in peritonitis which is supported by experimental facts. No recorded attempt by critical experiment to determine the nature of the emetic stimulus and to discover its manner of action could be found although the phrase "peritoneal irritation" was noted in practically every work upon peritonitis and vomiting. This present study was undertaken because of the apparent lack of proof that vomiting in peritonitis is really due to irritation of the peritoneum.

Although the emetic stimulus has usually been considered to be a nervous impulse, it was thought possible that it might either be a hormone or a toxin carried in the blood. Since emesis is induced by the direct application to the vomiting center of minute amounts of certain normal constituents of the blood, such as cholin and histamine, it is possible that when one of these is present in the blood in an increased amount, it may cause nausea and vomiting. In intestinal obstruction, which frequently complicates peritonitis, histamine may be present in the blood in abnormally large amounts, and, in such cases, may quite possibly constitute the stimulus to vomiting.

It is believed that observations recently made in this laboratory tend to exclude the probability of either a toxin or a hormone providing the important emetic stimulus in peritonitis. For example, in a series of 15 normal cats intraperitoneal injection of 10 cc. of a 50% turpentine emulsion produced vomiting within 6 seconds after the injection, a reaction time which seemingly would preclude a chemical stimulation of the center and yet be entirely within the limits of a reflex phenomenon. Furthermore, as will be described shortly, peritonitis failed to produce vomiting in 6 cats in which the vagus nerves had been divided in the thorax and the abdominal sympathetic and splanchnic innervation destroyed.