THE RELATION OF THE ENDOCRINE GLANDS TO OSTEOMALACIA.

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THE etiology of osteomalacia is still in doubt. Until about thirty years ago scarcely a guess was hazarded as to the cause of the condition. Until recently the theory of ovarian origin, originated by Fehling, has been generally accepted. Because of the rather frequent association with other disturbances, and because of the good results of various kinds of specific glandular therapy, other glands, singly or as a part of a pluriglandular disorder have been suspected of causing this disease.

There are three commonly described forms of osteomalacia, puerperal, rheumatic and senile, of which the puerperal form is by far the most frequent. Rickets and osteitis deformans would seem to be the result of a similar process, although the course and microscopic appearance may vary.¹

Histological and chemical investigations indicate that the process in osteomalacia consists in a replacement of normal bone that has undergone metabolism, by calcium-free or calcium-poor bone.²

Following the report in 1879 and 1880 of the good therapeutic effect on certain cases of osteomalacia, of removal of the pregnant uterus and ovaries as a complement to Caesarian section, Fehling recommended the procedure in the treatment of several cases of this disease.

Noting the good results of ovariectomy, he expressed the theory that osteomalacia was due to a pathological function of the ovaries leading to a vasomotor bone hyperemia which produces solution of the lime salts. Cristofolletti modified this view by assum-

ing that the endocrine function of the ovary lasts during pregnancy and causes a hypo-function of the chromaffin tissue. Falta⁴ regards as questionable the relation of the chromaffin tissue and metabolism.

Analysis, by McCrudden,² of the clinical results of castration in puerperal osteomalacia, indicate that whereas many cases were benefited or cured, a very large percentage of cases was not cured by the operation. While it might be suggested that the process continued even after the removal of the exciting ovaries, the return of malacia following a temporary cure after operation, the occurrence of the disease in non-pregnant women and before puberty as well as in males, speak against this hypothesis.

Although Wallart⁵ observed peculiarly marked development of the interstitial stroma cells in both pregnant and non-pregnant women, repeated, minute, histological examination of the ovaries, whether in the follicular apparatus, the germinal epithelium or the corpus luteum, has indicated no specific change.⁶

Although the theory of ovarian origin of osteomalacia appears untenable, the undoubted benefit of castration in many cases demands explanation. Castration, itself, according to most investigators, has no effect on the general metabolism.² Many cases recover spontaneously; others apparently improve as a result of varied treatment. The good results of castration are ascribed by McCrudden² to the prevention of future pregnancies. If this view is accepted the equally good result of X-ray sterilization and of normal and artificially induced labor is not surprising.

Evidence in support of Cohnheim's view that bones normally undergo active metabolism has steadily accumulated. Hanau⁷ pointed out that at ne-

cropsy, changes similar to osteomalacia are found in the pelvic bones of women apparently free from malacic symptoms. McCrudden² believes that osteomalacia is an exaggeration of a normal process, that when catabolism exceeds anabolism there is a tendency toward osteomalacia. He explains the prevalence of the disease in puerperal women as due to fetal demand for calcium. He emphasizes the occurrence of the disease usually after several rapidly succeeding pregnancies in poor women whose hygienic environment is bad. Occurring in non-pregnant women and in males, the disease is explained on the basis of increased calcium demand, from fractures, injuries, bone tumors and often from an unknown cause.

Biedl⁶ assumes that the principal role in the production of osteomalacia is played by the ovary (perhaps by the parovarium), and, judging by the incidence among men, by the testis. Male cases are relatively rare. In the castrated male patient reported by Elliott and Nadler⁸ the testes were normal upon histological examination. There was no retention of calcium or of phosphorus indicated in examination of the urine and stools of the week following operation as compared with that of the weeks preceding castration. Six months after operation pain was less marked, but chest deformity had increased. Five years after castration the process seemed at a standstill, although the bones showed no improvement upon X-ray examination.

The discovery of glandular interrelationships, especially between the ovaries and the thyroid and adrenal glands, suggested these glands in the part of pathogenic agent of osteomalacia. Hoennicke⁹ proposed a thyrogenic theory, which was amplified by

Parhon and Goldstein.¹⁰ While the evidence of abnormal thyroid function is present in many cases, it is as often absent. The insecure basis for this theory is shown by the fact that the authors have not decided whether a hypo- or hyper-secretion is responsible for the condition.

Parathyroid hyperplasia is common in osteomalacia, as it is also in normal pregnancy. Osteomalacia associated with hyperthyroidism and tetany has been reported. An association of tetany with rickets has long been recognized.

That the adrenal glands are concerned in the etiology of osteomalacia, was proposed by Bossi,¹¹ who reported the favorable influence of long continued subcutaneous injections of adrenalin. The glycosuric action of adrenalin and apparently also its action on the heart and vessels is strikingly slight in this disease.

Osteomalacia has never been reported in Addison's disease. Cristofolletti¹² collected 47 cases treated with adrenalin, 11 pregnant and 35 non-pregnant women. Of the former 45 per cent were cured and about 18 per cent improved; of the latter 17 per cent were cured and 40 per cent improved. Biedl asserts that there is no evidence that the adrenal cortex has a direct influence upon bone metabolism. It is not improbable that the pharmacodynamic action of adrenalin may account for the good results, which are the only evidence in favor of the pathogenic significance of the adrenals in osteomalacia.

Improvement has followed the injection of pituitrin in a few cases.¹³ Pal¹⁴ has reported improvement after the feeding of extracts of the anterior lobe.

Thymus gland, usually combined with phosphorus or other drugs, has seemed to be of value.

The view of Pommer that the central nervous system controls the development of osteomalacia, deserves, in the opinion of Falta, more attention than it has received, particularly because of the intimate relation of the central nervous system with ductless gland function.

It may, then, be said that in the present state of our knowledge, there is no real evidence that the frequent and manifold manifestations of endocrine disturbance occurring in osteomalacia, are a cause rather than an expression of the same metabolic disorder. Certainly, the action of no one gland or glands may be considered as causal factor. The conception of osteomalacia as an exaggeration of normal bone catabolism seems worthy of consideration. Further studies may indicate an influence of the endocrine glands upon such metabolism.

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COMMENT ON DR. NADLER'S ARTICLE

Dr. R. G. Hoskins, Chicago: The excellent summary of the evidence on the etiologic significance of the endocrine glands in osteomalacia, by Doctor Nadler, shows that as a mere matter of logic the commoner theories along this line are untenable. His conservative attitude is to be commended. It is a lack of such conservatism that has brought the endocrine literature into a disrepute that is, on the whole, deserved.

The fact that various of the internal secretions modify metabolic activities makes it probable that osteomalacia and other metabolic diseases are influenced by conditions in the endocrine glands. In view of this fact very definite evidence is needed to establish the existence of specific relationships in all such cases. That an operation like ovariectomy which supposedly exerts a marked influence on calcium metabolism should likewise affect the course of osteomalacia is not surprising. That other endocrine glands indirectly or directly play some part is probable. Further than this the evidence at present justifies no definite conclusion.

Dr. Frank E. Peckham, Providence, R. I.: From an orthopedist's standpoint it is clear that normally there is a metabolism going on in all bone. Growth is constantly taking place and waste products being thrown off. Bone physiology, like the physiology of all other structures in the body, is intimately associated with the endocrine organs. Some authors consider that the thyroid presides especially over the fixation of calcium and if its function is interfered with, there is an excess of elimination and hence a softened osseous system. Undoubtedly this condition is an etiological factor in some cases of scoliosis and may be relieved promptly by thyroid extract.

It is well established that the endocrine glands are very interdependent; the product of one organ stimulates the next one in line. Hence the therapeutic use of a single extract is not likely to be as effective as several given together. For the stimulation of calcium metabolism it has been shown that the adrenals exert some effect and that the thymus is also concerned with the retention of calcium by the body. Clinically good results have been obtained in the treatment of osteomalacia by giving pituitary extract.

As a matter of fact our knowledge of endocrinology is not yet what it ought to be; but theoretically, at least, pluriglandular treatment should be preferable to single gland medication; and in osteomalacia and in other disorders of bone physiology, such combined treatment is probably still the most logical at our disposition.

Dr. Charles A. Elliott, Chicago: In discussing the relationship that may exist between the endocrine glands and osteomalacia, one is forced to state at the outset that there is no demonstrated proof at present that any such relationship exists. However, the theory of such relationship is the most attractive explanation of the phenomena observed in this disease.

Osteomalacia has been demonstrated to be a disease in which there exists, as the most striking phenomenon, a disturbance in the metabolism of the alkaline earths, notably calcium and magnesium, but as to the cause of such disturbed metabolism there is no unchallenged theory. The theory, first elaborated by Fehling, that the ovaries are the causal factor in the production of osteomalacia, has been abundantly disproved, but the value of the operative procedure advanced by him, namely castration, has been demonstrated beyond a doubt for all of the cases in the puerperal group. The beneficial results of this procedure, however, do not lie in the supposed specific influence of the ovaries upon metabolism, but rather in the prevention of future pregnancies, during which time osteomalacia is prone to progress.

To my mind the best argument in favor of osteomalacia being a disease of disturbed function of the endocrine glands is found in the comparison with the analogous relationship that exists between thyroid function and metabolism in general, a matter that has been abundantly proved. If metabolism in general is regulated by the endocrine system, it seems likely that the disturbance in calcium and magnesium balance, as seen in osteomalacia, reasonably may be assumed to be due to a disturbance of a similar endocrine function.