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### **Comparable cell changes in central nervous system in cretinism, parathyroid tetany and fatigue.**

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Representative sections from the motor cortex, thalamus, mid-brain, cerebellum, medulla oblongata and cervical enlargement of the spinal cord, from each of five cretin lambs and two cretin goats were studied microscopically. A modification of Nissl's method was employed. Comparable preparations from three normal animals of the same sex and age (twins of three experimental animals) furnished the control material. The primary purpose of this series of investigations was to determine the nature and course of the nerve cell changes in the central nervous system following the experimental removal of the thyroid glands, and to attempt to correlate these findings with the well known symptoms of athyreosis, many of which are referable to central origin.

It was further desired to compare the nerve cell pictures presented in these cases with those from pathological conditions of quite different etiology and symptomatology in order to determine more fully the nature and degree of specificity of the reaction. To this end the affection of parathyroid tetany was selected, almost the antithesis of the first named condition. If chromatolysis follows in the latter event where neuromuscular activity is frequently at its maximum, should we expect to find a piling up of the extranuclear chromatin in the former where the symptoms are so strikingly opposite in character? Nissl preparations were made from the brains and spinal cords of thirteen

dogs in which tetany had been induced experimentally. These were taken from the same levels as described above for the cretin animals.

For further analysis the comparison was extended to cell changes in the central nervous system as a result of functional activity. Fatigue was induced in sixteen white rats by forcing them to swim in a tank of warm water (body temperature) for periods varying from fifteen minutes to six hours.

Such a comparative study has revealed, in each case, a definite but somewhat variable chromatolysis. No marked variations in the nature and course of the affection were found to follow these conditions so strikingly opposite in character. From the material at hand, the type of reaction was clearly quite independent of the seat of action or nature of the opposing condition. It was a question of quantitative rather than qualitative variation from the normal. Cellular alterations representative of steps in the course of the reaction were readily recognized. The severity of the visible symptoms (tetany, cretinism and exhaustion) was the constant guide in selecting these types. To demonstrate the consecutive stages found and the correctness of the conclusions drawn from them, twenty-four slides were shown.

Early in the chromatolytic reaction, as measured by the severity of the external symptoms, the cells stain more deeply than normal. This intense staining is found in the nucleus as well as in the cell body, but usually in a less marked degree, and cannot be entirely accounted for by the accompanying shrinkage which is almost invariably associated with it. There is either an actual increase in the amount of extranuclear chromatin or an increase in the affinity of this substance for the basic stains. The intensity of the stain is too great to be explained otherwise. At an early stage a part of this substance is dissolved in the cell fluids, even within the nucleus, rendering all outlines extremely indistinct at times. The maximal expression of this condition is reached at a relatively early stage in the process. This is evidenced by the fact that it invariably appears after thirty minutes of activity, in mild cases of cretinism and in mild parathyroid tetany. It is soon followed, however, by a progressive fragmentation and dissolution of the Nissl substance, which begins, as a rule, in the perinuclear zone and spreads toward the periphery. In fact this process most probably begins much earlier. In the more acute affections, fragmentation seems to take the lead (severe para-

thyroid tetany). In less severe cases, however, (mild tetany, cretinism and functional activity) solution of the granules almost keeps pace with the initial fragmentation. This reaction is indistinguishable under each of the above mentioned conditions. The ultimate expression of this alteration is shown in cells almost devoid of extranuclear chromatin. That which remains is reduced to a very fine state as can be seen from the dust-like consistency of these particles. They possess little or no affinity for the basic stains. In this state of the cell, the contour and outlines become more indistinct.

The nucleus, on the other hand, seems to have maintained its integrity to a greater extent. Other than being slightly swollen and clouded, as described above, it appears quite normal. Complete karyorrhexis and karyolysis was met with in one case only, so little significance can be attached to it. Shifting of the nucleus toward the periphery of the cell occurred no more frequently in the experimental than in the control tissue. Vacuolization of the cytoplasm commonly accompanied the most acute affections, particularly in the Purkinje cells and granule cells of the cerebrum. This was often accompanied by perivascular and pericellular oedema.

From these investigations, chromatolysis has been interpreted as a general reaction of nerve cells; a reaction induced in these elements by conditions opposed to their normal functional equilibrium. If carried beyond certain physiological bounds, this reaction may be looked upon as pathological and extreme conditions result in degeneration and death of the cell. The severity of the opposing factors, and consequently the rapidity with which the changes are produced, do exercise a profound influence, but express themselves quantitatively rather than qualitatively. This point of view was expressed by Van Gehuchten<sup>1</sup> some years ago.

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<sup>1</sup> Van Gehuchten, *La Cellule*, 1897, xiii.