# Histological Effect of Chlorpromazine on Nissl Substance and Golgi Apparatus of Cortical Neurons. (24181)

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Holtet(1) reported a marked depletion of Nissl substance, especially in the large pyramidal cells in the cerebral cortex of the albino rat, following administration of chlorpromazine in doses ranging 20 to 60 mg/kg/day for 3 days. He presented several photomicrographs of large pyramidal cells, stained with Einarson's gallocyanin-chromalum method, which were completely devoid of Nissl substance and showed marked swelling of neurons. This he believed was a reaction to injury and that chlorpromazine in some way interfered with metabolism of Nissl bodies. This work stimulated us to attempt to confirm these observations and to study other possible abnormalities in cytological structure of the cortical neurons.

*Materials and methods.* Twenty-eight C57 mice received 15 mg/kg/day chlorpromazine* subcutaneously for 28 days. Fourteen mice received placebo injections for same period. On 29th day the mice were decapitated, the cranial vault emptied and the contents placed in appropriate fixatives. In addition 3 adult Osborn-Mendel rats were injected interperitoneally with 25 mg/kg of chlorpromazine 3 times a day for 3 days. Three control rats were injected with an equivalent amount of placebo. On the 4th day the rats were sacrificed in the same manner as mice. Mouse tissue was stained by Einarson's gallocyanin-chromalum technic(2) and also with toluidine blue. Rat brain sections were stained for Nissl bodies utilizing the gallocyanin-chromalum method and the methyl-green pyronin Y method of Long and Taylor(3). Golgi apparatus in both mouse and rat tissue was stained by silver techniques of Kruszynski(4) and the method of Elftman(5), followed by gold toning.

*Results.* Following injection of chlorpromazine, the animals became quite lethargic, indifferent to their surroundings and appeared to be sleeping, however they were easily aroused by handling. Despite this dramatic change in behavior there were no detectable differences in Nissl structure of the experimental animals when compared to their controls. The sections stained by Einarson's gallocyanin-chromalum method, methyl-green pyronin Y method, and the toluidin blue technic revealed essentially normal dense clumps of chromophilic substance in the cytoplasm of pyramidal cells of the cortex. As a control on staining procedures, several sections were washed in 1% ribonuclease for one hour at room temperature. In these sections the pyramidal cells were completely devoid of stainable Nissl substance.

The Golgi apparatus in cortical cells of experimental animals appeared essentially normal, presenting a fine perinuclear reticulum, but in some cells the network was broken up somewhat into fine granules. We failed to demonstrate any consistent changes in Golgi apparatus of the pyramidal cells of either the experimental mice or rats.

*Discussion.* In dogs chlorpromazine is concentrated primarily in the brain(6). Using $S^{35}$ labeled chlorpromazine, Christensen and Wase(7) further showed a marked uptake by the brain in 30 minutes, maintained for 2 days with maximal excretion in urine occurring in 4 to 24 hours. The exact site and mechanism of action within the brain, however, is still in doubt. Lehmann(8) contends that the site of action is in the ventral region of the thalamus, in the brain stem, in the subthalamic nucleus, red nucleus, substantia nigra, hypothalamus, and the pontile tegmentum, while Himwich(9) believes the posterior hypothalamus and the midbrain reticular gray are primarily involved.

After completion of this work, however, we learned by personal communication with Dr. Larus Einarson, in whose laboratory Holtet's

* Generously supplied by Smith, Kline, and French Laboratories as Thorazine.

work was done, that upon reevaluation of their data they felt that these results were due, at least in part, to traumatization to the animals during injections of the drug. This leaves Grenell's(10) observation that the nucleic acids are reduced in chlorpromazine treated rats unconfirmed. It is, of course, possible that these biochemical alterations in nucleic acids are insufficient to be detected by the usual histochemical technics.

*Summary.* In mice receiving 15 mg/kg/day of chlorpromazine for 28 days and in rats receiving 25 mg/kg of the drug 3 times a day for 3 days, no morphological alterations in the Nissl and Golgi bodies of the cells of the cerebral cortex were noted.

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## Observations on Toxins of Poisonous Fishes.* (24182)

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Certain fishes of the tropical Pacific, including fish as diverse as puffers (*Tetraodon*) and snappers (*Lutjanus*), have long been reported to be highly toxic when eaten. Hiyama(1), by feeding tests, and Halstead and Bunker(2), by intraperitoneal injections into mice of aqueous extracts of fish viscera and flesh, have confirmed these reports. This toxin is not the result of bacterial decomposition, but occurs in the flesh of fresh fish. These toxins may vary among the different species(3). The object of these tests was to explore the nature of the toxin sufficiently to permit planning of future studies on poisoning characterized by Halstead(3) as *Ciguatera*. Fish producing this syndrome are reported by islanders to be highly toxic in certain restricted areas, but elsewhere are excellent as food. To avoid any confusion of toxins that could be different, only body muscles of *Lutjanus bohar* Forskal from Palmyra were used.‡ About 20 fish were tested ranging 14 to over 24 inches long. Only fish longer than 16 inches produced the syndrome characteristic of *Ciguatera* poisoning.

*Results.* The first phase was to find an animal that would respond consistently with symptoms paralleling those found in man. Cats so responded, as reported by others, but were not readily available. A variety of other vertebrates was then tested, but none except the imported mongoose (*Herpestes javanicus auropunctatus*) responded to dosages, in terms of body weight, that caused paralysis and death in cats. The symptoms of the mongoose, like those of the cat, included loss of certain reflexes, for example, failure to withdraw the foot when touched lightly. A progressively severe loss of coordination followed in first the back and then the forelegs which, in acute cases, would prevent the mongoose from standing or righting itself after falling. Death, preceded by coma and

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