MORPHOLOGICAL CHANGES IN THE NERVOUS SYSTEM IN TETANUS

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Reports describing the cytological changes in the nervous system caused by tetanus toxin are highly conflicting. No clear answer is given to the question of the character of these changes, their depth, the specificity of their selective localization, or the degree of their reversibility. In recent years it has been insisted increasingly that tetanus toxin—one of the strongest neurotropic poisons—causes profound degenerative changes in the nerve cell [2]. Changes detected in the anterior horn cells of the spinal cord in the first experimental investigations were interpreted as specific [5, 8, 9, 11]. Later workers found no morphological changes in the central nervous system in tetanus, and they attributed the pathological changes sometimes observed to the action of therapeutic agents and hyperthemia or regarded them as postmortem changes [3, 6, 12]. With improvements in experimental techniques, marked changes began to be discovered in the gray matter of the spinal cord, the spinal ganglia, and the sciatic nerves [7]. More recently still [4] the application of luminescence microscopy and of histochemical techniques revealed irreversible changes in the cells of the intermediate zone of the spinal cord of rats with experimental tetanus.

The authors have studied the pathomorphological changes in the nervous system of dogs with experimental tetanus poisoning; subsequently these techniques were used to study human subjects dying from tetanus.

EXPERIMENTAL METHOD

Tetanus toxin was injected intramuscularly (into the upper third of the leg) into 10 dogs and intravenously into 3 dogs in doses of 3 MLD per animal. When the intravenous method was used, and also after the intramuscular injection of large doses of toxin (3 dogs received 15 MLD each), generalized ascending tetanus developed very rapidly: marked opisthotonus was present at the end of the 2nd day, accompanied by muscular rigidity, and a disturbance of the functions of the oculomotor nerves manifested as convergent or divergent strabismus (Fig. 1). The animals were sacrificed at the climax of the acute period by injection of ether into the heart.

The nervous system was extracted, fixed, and then investigated as described by B. S. Doinikov [1], using various neurohistological methods.

EXPERIMENTAL RESULTS

The internal organs were invariably congested. Congestion of the meninges and brain was especially marked after intravenous injection of the toxin. In two cases, focal pneumonia was found in the lungs. Histological examination revealed marked circulatory disorders (atony, tortuosity of the vessel walls, blood cells in their lumen). Hemorrhages were observed around the vessels, with foci of protein exudation and, particularly commonly, zones of perivascular edema. The brain tissue was edematous, especially in the cerebral hemispheres, and areas of denudation of nerve cells were seen in the cortex. Ghost cells could be seen in and around these areas (Fig. 2). The most constant findings in the brain were scattered, fine chromatophilic granules (sometimes with a double outline), chromatolysis, and staining of the processes of nerve cells at a considerable distance. The changes described were found more frequently in the frontal lobes. In some cases, the cytoplasm of the nerve cells was vacuolated, and their nuclei contained paranucleolar bodies. The cell bodies were sometimes round in shape. In isolated areas of the cortex

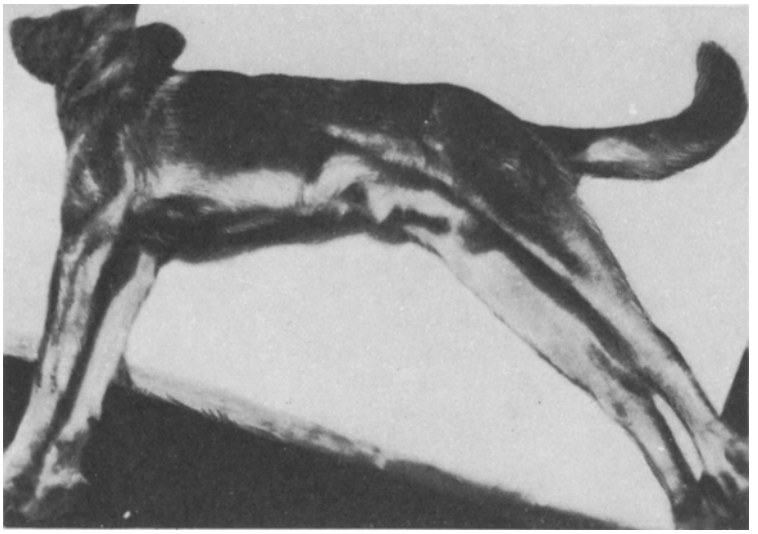

Fig. 1. Opisthotonus in a dog with experimental tetanus poisoning.

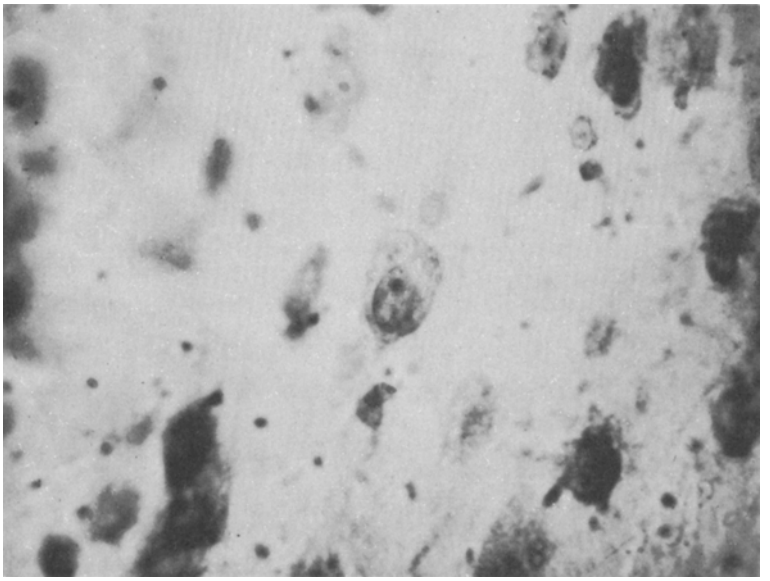

Fig. 2. Marked chromatolysis and vacuolation in the cells of the cerebral cortex and ghost cells in a dog on the 5th day of the disease (after injection of 3 MLD of tetanus toxin). Photomicrograph. Stained with thionine by Nissl's method. Magnification 400x.

groups of intensively stained, long cells were observed, and occasionally the nerve cells were surrounded by clusters of satellites. Neuronophagy was very rarely seen.

In the hippocampus zones an absence of cells and chromatolysis were found, and were especially common in the region of the sector of Zoemmerov. Ghost cells were also seen here, and the cell nuclei were intensively stained. Chromatolysis, scattered granules of chromatophilic substance, and occasionally hyperchromatism were observed in the cerebral peduncles, in the cells of the oculomotor nerves and the red nuclei. The cells of the substantia nigra showed a reduction in the amount of pigment, which was situated outside the cells. In the basal ganglia changes similar to those observed in the cerebral cortex were predominant in the caudate nucleus and thalamus. The pons was affected less than the other parts of the brain stem, but signs of acute involvement of the pontine nuclei were seen. In the cerebellum some of the Purkinje cells were lost; the cells which remained showed intensive staining

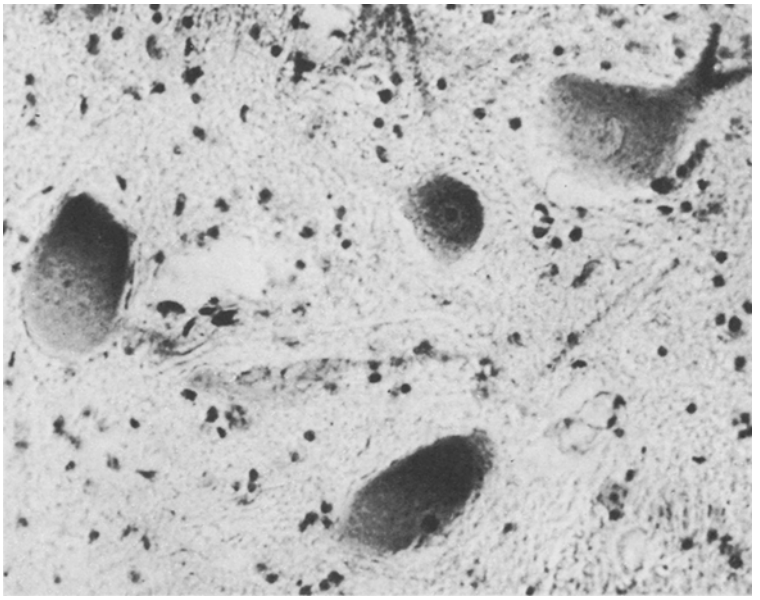

Fig. 3. Severe swelling (in some cells having progressed into a severe lesion) of the ventral horn cells of the spinal cord of a dog on the 5th day of the disease (after injection of 3 MLD of tetanus toxin). Photomicrograph. Stained with thionine by Nissl's method. Magnification 200×.

and chromatolysis, the latter extending to the body and the initial part of the process. The processes themselves sometimes had the appearance of stags' horns. The nuclear membrane was thickened, and the nucleus was frequently converted into clumps of material. The neuroglia was usually juicy and showed signs of proliferation. In the medulla the nuclei of the vagus nerve, the common motor nucleus with the glossopharyngeal nerve, and the inferior olives were the parts most severely affected. In some cases the reticular formation was badly damaged. In two dogs asymmetry was observed in the lesions of the nuclei of the 9th and 10th pairs of cranial nerves: on the side of injection of the toxin the cells were smaller in size and more intensively stained. In the motor cells of the ventral horns of the spinal cord, the hyperchromatosis was more marked on the side of injection; sometimes marginal chromatolysis and vacuoles were seen here (Fig. 3). Examination of the spinal cord revealed very severe lesions in the intermediate zone and the dorsal roots: chromatolysis, elongated cells, and fragmentation of the processes were often seen. The sensory (spinal, Gasserian) and sympathetic ganglia were only slightly affected: chromatolysis was observed only in individual cells, and paranuclear bodies were occasionally found.

The pathological changes in the peripheral nerves were minimal. Only a slight proliferation of the neuroglia was observed in the cytoplasm of the Schwann cells, with vacuole formation.

In order of severity of the lesions discovered, the parts of the nervous system investigated could be arranged in the following manner: the cerebral cortex, hippocampus, cerebellum, basal ganglia, mesencephalon, medulla, spinal cord, sensory ganglia, peripheral nerves. Most of the cells, however, retained their normal structure, and the changes were mainly those generally regarded as reversible. The intravenous injection of the toxin, and also the intramuscular injection of large doses, causing the more violent development of tetanus, were accompanied by a more extensive involvement of the nerve cells, corresponding to the type occurring in the acute or ischemic disease. However, it is difficult to draw any conclusions regarding the specificity of the changes observed in tetanus, for the reaction in the various components of the cells described above is also observed in other diseases accompanied by convulsions and hypoxia [1]. The present results showed that in tetanus the state of affairs is rather one of widespread changes involving all divisions of the nervous system and generally reversible in character. These changes are evidently associated mainly with the convulsions, the respiratory and cardiovascular failure, and the hypoxia.

In the spinal cord the lesions were found mainly in the intermediate zone of the gray matter; the brain stem also was severely affected, in agreement with data in the literature [4, 10]. It is concluded that the results of these pathomorphological investigations confirm the widely held conception of the central origin of the convulsive syndrome in tetanus.

The changes revealed by the present experiments on dogs were mainly in agreement with those observed in patients dying from severe forms of tetanus. The nervous system was studied in detail in 16 patients after death. In many cases the material was taken and fixed very soon after clinical death had been diagnosed; in this way the development of postmortem changes was prevented to a considerable extent.

With the introduction of new methods of treatment of tetanus (specialized treatment in respiratory centers with the use of the principles of resuscitation, neuroplegics, and muscle relaxants), asphyxia due to convulsions is no longer the principal cause of death. In this series the patients died from secondary complications, mainly pulmonary, accompanied in every case by the development of severe hypoxia. Changes were detected in the nerve cells resembling the type found in the severe ischemic disease, and in particular, in the acute type of this disease. The lesions were situated predominantly in the cerebral cortex, the basal ganglia, hippocampus, mesencephalon, cerebellum, hypothalamic region, and the internuncial neurons of the spinal cord. In addition, circulatory changes were discovered in the form of atony and dilatation or, conversely, collapse of the walls of the capillaries. Zones of perivascular edema and sometimes small hemorrhages were observed around the vessels. No infiltrative changes were found. A clinico-morphological comparison showed that the pathological changes in the central nervous system were the more severe the deeper the level of hypoxia arising as a result of the pneumonia, pulmonary atelectasis, and cardiovascular failure.

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