PATHOLOGY OF TESCHEN DISEASE
(VIRUS ENCEPHALOMYELITIS OF SWINE)*

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Teschen disease, a viral encephalomyelitis of swine, was first described in 1930 by Treffny during an epidemic in Teschen (Tesin), Czechoslovakia. It seems, however, that the disease was not unknown among veterinarians who, previous to this, had observed occasional sporadic cases of paralysis in pigs. Since 1930, it has been enzootic and frequently epizootic in Eastern Europe, but has never been known to occur in the United States. Klobouk first demonstrated its viral etiology in 1931, and during the next decade a number of pathologic and virologic studies were reported by Czech and German veterinarians. These have been reviewed by Lépine and Kaplan and Meranze.

The present study of the pathology of Teschen disease was stimulated by frequent statements in the literature that a similarity existed between this disease and human poliomyelitis, both pathologic and otherwise. Dobberstein, who has reported the most extensive histopathologic investigations up to 1942, was of the opinion that the two diseases bear a close resemblance and he went so far as to speak of Teschen disease as “poliomyelitis of swine.” A study of the pathology of Teschen disease was, therefore, undertaken with emphasis on the development and distribution of the lesions in the central nervous system. We also undertook to compare the pathologic changes with those of poliomyelitis and other viral encephalomyelitides, such as the equine, St. Louis, Japanese B, and louping-ill types. A preliminary report of the involvement of the central nervous system after intracerebral inoculation of Teschen virus has appeared as has also a paper dealing with highlights of the pathology of the central nervous system in Teschen disease and a comparison with human poliomyelitis.

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† For this reason, the importation of the virus into the United States is forbidden. All work with the agent, reported in this paper, was carried out in the Virus Laboratory of the 98th General Hospital, U.S. Army, Europe.

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Materials and Methods

The material examined was obtained from some 300 pigs which were used during the course of a series of virologic studies on Teschen disease. Several strains of virus* were introduced intracerebrally, intranasally, and orally into pigs which were 4 to 6 weeks old.

The animals were sacrificed at different stages of the disease. Eleven were sacrificed as soon as they manifested an elevated temperature, which was interpreted as the earliest clinically detectable stage of the disease. The majority of the animals were killed at the height of the disease, which corresponded to the second or third day of fever, at a time when spasticity, convulsions, and often coma were present. If these animals had not been sacrificed, they would have died spontaneously within 24 hours. Since the mortality from the disease was extremely high, only 2 animals reached the convalescent period. They were sacrificed 1 month after the onset of the disease.

The distribution of the lesions in the central nervous system was determined in the following manner. Serial sections through a normal pig brain and spinal cord were made. An enlarged sketch was then made from each level of the central nervous system and a number of photographic copies of each sketch were made. Serial sections of the brain and spinal cord from each animal were examined, and concurrently the distribution of the lesions was plotted on the photographic sketch, which corresponded to the level of the microscopic section being studied. This was done on material secured from animals which were inoculated intranasally, intracerebrally, and orally. In this manner comparative distribution of the lesions in the various levels of the central nervous system was made evident.

The usual neuropathologic techniques were employed. The brain and spinal cord, and dorsal root, sympathetic, and gasserian ganglia of a number of animals were sectioned serially after embedding in celloidin.

Clinical Features

The disease in pigs, whether naturally occurring or experimentally induced, runs the course of a severe encephalomyelitis with a high mortality. The characteristic signs, in the order of their appearance, are fever, tremors, opisthotonos, stiffness of the extremities, ataxia, convulsions, paralysis of the cranial nerves, and weakness or paralysis of the extremities (Text-fig. 1). The incubation period varies with the

* For these strains of Teschen disease virus we are indebted to the late Dr. Frantisek Gallia, National Institute of Health, Prague; to Dr. Sven Gard, State Bacteriological Institute, Stockholm; and Dr. Pierre Lépine, Pasteur Institute, Paris.
route of inoculation, but usually falls within 6 to 15 days.\textsuperscript{17} Of many laboratory animals tested, the only susceptible hosts seem to be the pig and the wild boar.\textsuperscript{17,18}

**THE PATHOLOGIC CHANGES AND THEIR DEVELOPMENT**

In many animals at the height of the disease the abdominal and thoracic organs revealed moderate to slight hyperemia. In some pigs there were tracheobronchitis, swelling of the spleen, and cloudy swelling of the liver. Occasional foci of pneumonia were noted.

The important morphologic manifestations of Teschen disease occur only in nervous tissue. Grossly, the brains of the animals killed at the height of the disease revealed edema of the meninges and congestion of the meningeal and cerebral vessels.

**Early Stages of the Disease**

Mild, focal, lymphocytic meningitis (Fig. 1) was a constant finding at the base of the brain. Polymorphonuclear leukocytes as the predominant cell type in the inflammation of the cerebral meninges were
seen in only one case. Also, moderate lymphocytic meningitis over the cerebellum was one of the earliest manifestations of Teschen disease. Over the cerebrum meningitis was less pronounced.

Mild lymphocytic infiltration was seen occasionally around small vessels of the first cerebral layer, as well as a few cell nodules, which occurred chiefly in the rhinencephalon. Moderate perivascular lymphocytic infiltration in the molecular layer of the cerebellum was a further early manifestation. In only 2 of the cases examined during the early stages of the disease were marked focal infiltrations composed predominantly of polymorphonuclear leukocytes seen in the molecular layer and in the meninges of the cerebellum.

At this time nerve cell changes in the cerebellar cortex, dentate nucleus, and roof nuclei either were not present, or were found only occasionally in the Purkinje cell layer and molecular layer and were minimal.

In the pons and medulla a few cell nodules and infiltrations were observed around the small vessels.

The spinal cord was without lesions in the majority of the cases. In 2 animals, in addition to the cerebral and cerebellar involvement, lesions were found in the anterior horn of the cervical cord, but not in the thoracic, lumbar, or sacral cord.

Only in one animal was found involvement of the anterior horns at all levels. In that case the destruction of the nerve cells (Figs. 2 to 6) was characterized by varying patterns of dissolution (chromatolysis) of the Nissl substance. The pattern of the Nissl substance became hazy and later dust-like, but at the periphery of some of the neurons and in the neuronal processes it remained well preserved. At this stage of the degeneration the nucleus frequently revealed slight hyperchromatism of its membrane and of the small dust-like particles in the nucleoplasm. This form of degeneration can occur also at the height of the disease. Degeneration of the cytoplasm might progress until the Nissl substance had completely disappeared. The cytoplasm of such cells was either basophilic or metachromatic to toluidine blue and might be swollen. Cytoplasmic vacuolization starting at the periphery and finally involving the whole cell body often was seen.

The anterior horn of the same animal in some sections was densely infiltrated with polymorphonuclear leukocytes which were actively phagocytizing dead nerve cells. In other levels of the cord, in addition to the degeneration of the nerve cells, a few neuronophagic and cell nodules and a moderate degree of perivascular infiltration were present. The microglia in the anterior horn showed marked proliferation.
The cells at first formed rod-like elongated or twisted elements (Fig. 7). However, especially in the early stages of the disease, marked degeneration of nerve cells accompanied by disproportionately moderate glial proliferation and slight perivascular infiltration might be seen in various levels of the spinal cord.

**Midcourse of the Disease**

**Spinal Cord.** Lesions were found localized in the anterior horns and in the posterior horns as well (Fig. 8). No differences in the involvement of the cervical, thoracic, lumbar, and sacral regions were observed.

One of the most characteristic features was the intense destruction of nerve cells and the presence of many neuronophagic and cell nodules in the cord. Often the cell nodules occurred in the neighborhood of vessels. Microglia were considered to be the predominating cells in neuronophagic and cell nodules; in these formations oval forms of these cells were the most frequent type encountered. Lymphocytes, in particular, always intermingled with microglial cells in areas of neuronophagia and in cell nodules. Many of the dead nerve cells were removed by phagocytosis (Fig. 9); others, especially those which were acidophilic in sections stained with hematoxylin and eosin, might occasionally undergo dissolution and be converted into a fluid-filled cavity.

Often the neuronal changes were more prominent in one half of the cord segment, while in the other half at the same level the proliferation of the glia or the perivascular infiltrations, or both, were prominent. The many mitotic figures were further evidence of the prolific activity of the microglia. Diffuse and nodular proliferation of microglia occurred also in areas where perivascular infiltrations were absent. The macroglia did not react as actively as the microglia. Hypertrophic astrocytes, however, were observed among the diffusely proliferating microglia and in the cell nodules.

There was a marked lymphocytic infiltration in the Virchow-Robin spaces of the involved areas. In addition to lymphocytes, a few plasma cells and histiocytes sometimes were seen. Lymphocytes and plasma cells might occur diffusely distributed in the anterior horn as well. Marked perivascular infiltrations were present in the white matter. Perivascular infiltrations occurred also in areas where neuronal damage was absent. The blood vessels were markedly congested. Very rarely, small hemorrhages occurred around the vessels.

The myelin of the intramedullary anterior root fibers was unaltered,
and gitter cells were not found. Bielschowsky staining revealed the neurofibrils to be well preserved in the early stages of neuronal damage. With progression of the degeneration of the nerve cells the neurofibrils of the cytoplasm became indistinguishable and finally disintegrated and disappeared.

Material fixed in Zenker's solution and formalin and stained with hematoxylin and eosin and Giemsa's stain was examined for inclusion bodies. Neither intranuclear nor cytoplasmic inclusions were present in the cord or in other regions of the central nervous system.

Perivascular infiltration and cell nodules also occurred in the posterior horn, although less frequently than in the anterior horn. Neuronal damage in the posterior horn was not found.

A slight lymphocytic meningitis usually was present in the diseased cervical, thoracic, lumbar, and sacral segments, and often its distribution was focal rather than diffuse.

Medulla Oblongata. Generally, the morphologic manifestations of the process at the level of the medulla oblongata were minimally different from those seen in the cord. The manifold degenerative forms of nerve cells, which were associated occasionally with slight glial and mesenchymal reaction, were not seen as often as in the cord, nor were areas of neuronophagia as prominent. On the other hand, perivascular cuffing and cell nodules were relatively more outstanding.

Pons. The lesions of the pons were quantitatively less pronounced than in the cord. There was not such a variety of neuronal degeneration nor were areas of neuronophagia so widespread. On the other hand, cell nodules and perivascular infiltrations prevailed here. The meningeal reaction was slight and consisted of a few lymphocytes and plasma cells.

Cerebellum. Marked changes occurred in the cerebellar cortex, especially in the Purkinje and molecular layers. The dentate nucleus and the roof nuclei also were involved. Meningitis was very marked in the cerebellum at the height of the disease. Dense infiltrations of lymphocytes and plasma cells were present, particularly in the sulci.

The Purkinje cells underwent considerable swelling and total vacuolization (Fig. 10); there was simultaneous retraction of the nuclear contents from the nuclear membrane, and the nucleus revealed granular hyperchromatism or a pastel-like basophilic discoloration. These nuclei soon perished. In the center of the pale vacuolated Purkinje cell one might find scant remnants of chromatin. Another change seen in the Purkinje cell was similar to Nissl's "akute Zellerkrankung," although the cell processes were not visible over long distances and the
outlines of the cell were not as distinct. Slight retraction of the cytoplasm from the surrounding tissue and of the nuclear contents from the nuclear membrane occasionally was present. Similar neuronal changes were seen in the molecular layer, although liquefaction of nerve cells was not as marked as in the Purkinje cells.

Large rows of Purkinje cells were destroyed (Fig. 11). Their former position was indicated by enormous proliferation of the microglia. Many “Strauchwerke” in the molecular layer indicated phagocytosis of the Purkinje cell processes. In many areas these formations fused into an extensive, diffuse, microglial proliferation. The bodies of the necrotic Purkinje cells were phagocytized by extensive nodular accumulations of microglial elements. Numerous areas of neuronophagia and of cell nodules were present (Fig. 12) in the molecular and Purkinje cell layer. In many instances it was difficult to distinguish between lesions of these two types, especially since the neuronophagic formations very often became confluent. Cell nodules of varying size also were present in the granular layer. Perivascular infiltrations were very marked, particularly in the molecular layer but also in the Purkinje cell layer.

Mesencephalon. Infiltrations and cell nodules were regularly found in the corpora quadrigemina. Usually perivascular infiltration was more severe in the substantia nigra than in the nucleus ruber; both nuclei, however, were involved at the height of the disease. In the majority of our cases the gray matter around the aqueduct revealed fewer lesions than the mesencephalic regions just mentioned.

Diencephalon. The diencephalon was regularly involved at the height of the disease. There were many foci of perivascular infiltration composed chiefly of lymphocytes, and cell nodules were very often found. Comparisons of the symmetrically cut thalami sometimes revealed marked loss of nerve cells on one side only. A large number of nerve cells in the thalamus underwent vacuolization of a type similar to that of the Purkinje cells. Vacuolization usually started at the periphery with retraction of the cytoplasm from the surrounding tissue. Neuronophagia of these dying cells was rarer in the thalamus than in the cerebellum. This was true also in regard to the glial reaction around these nerve cells. When complete vacuolization of many nerve cells occurred, large thalamic areas appeared perforated, the surrounding tissue might shrink and collapse, and occasionally cone-like microglial proliferations from the periphery of the cavity toward its center were seen. However, perivascular infiltration and cell nodules rather than the degeneration of the parenchyma dominated the
anatomical picture. Diffuse glial proliferations were not seen as often here as in the cerebellum.

Constant and marked manifestation of the disease was present in the subthalamus, the hypothalamus, and around the third ventricle. Here, as in the thalamus, perivascular infiltration and cell nodules prevailed; degeneration of nerve cells similar to the thalamic vacuolization was not observed in the hypothalamus.

Occasionally, a few perivascular infiltrations and cell nodules were present in the internal capsule.

_Globus Pallidus, Putamen, Caudate Nucleus, and Claustrum._ Infiltrations and cell nodules were found in the globus pallidus, putamen, caudate nucleus, and claustrum in decreasing order of severity. These nuclei were less severely involved than the diencephalon and mesencephalon.

_Cerebral Cortex._ The cortex revealed a moderately large number of loosely formed cell nodules and perivascular infiltrations (Fig. 13). These changes were most marked in the rhinencephalon. Definite regressive changes in nerve cells and areas of neuronophagia were rarely seen. In the cortex one might find shrunken nerve cells resembling the change described by Nissl as "chronic neuronal disease"; it is known that these shrunken neurons may occur in normal experimental animals.19

_Peripheral Ganglia._ The gasserian, cervical, stellate, thoracic sympathetic, and celiac ganglia of 34 animals, 3 of which were controls, were examined. At the height of the disease slight to massive infiltrations, composed chiefly of lymphocytes and less often of plasma cells, were found in the interstitium of the ganglia of 22 animals. These foci of infiltration, notably in the gasserian ganglion, were often nodular. In many cases the extent and severity of infiltration seemed to increase with longer survival after the onset of signs.

Foci of infiltration were marked in the gasserian, cervical, and celiac ganglia and were slight or absent in the stellate and thoracic sympathetic. In 3 of our 34 cases, the gasserian and cervical ganglia showed marked participation of polymorphonuclear leukocytes in the inflammatory process. In another case there were more plasma cells than usual.

Marked degenerative changes occurred occasionally in the neurons of the ganglia in Teschen disease. They were found most often in the gasserian, less so in the cervical, and rarely in the celiac ganglion. Definite neuronal degeneration was not seen in the thoracic sympathetic or stellate ganglia. The Nissl substance of the degenerated nerve
cells was dust-like and was concentrated at the periphery of the cell; often the perinuclear parts were slightly metachromatic. The nucleus of these chromatolytic nerve cells either was swollen or shrunken; the nucleolus usually was swollen. In later stages of degeneration the outlines of nucleus and protoplasm became indistinct. In addition to the neuronal degeneration, one saw early changes in the amphicytes of the capsule. These increased in number and size. By proliferation, they replaced the dying nerve cells until the whole capsule was filled with progressive amphicytes which often were mixed with proliferating connective tissue elements and lymphocytes. These proliferating cells might later decrease in number leaving a shrunken formation, the so-called residual nodule. Extremely rarely, neuronophagia of dead nerve cells by amphicytes was seen.

The spinal ganglia revealed degenerative neuronal changes and lymphocytic infiltration similar to those already described in the peripheral ganglia.

Convalescent Stage of the Disease

Corresponding to the findings in the acute stages of the disease were the changes seen in the convalescent animals. Two animals which survived showed cerebellar atrophy (Fig. 14), which in many folia was restricted to the Purkinje-cell layer. In other areas, however, many nerve cells in all three cerebellar layers had disappeared and a marked isomorphic gliosis was present. The external form and structure of the cerebellum were preserved. The molecular layer was decreased, the Purkinje cells were missing over large areas, and the granular layer was diminished. The Bergmann glia became multilayered and took the place of the Purkinje layer. In the atrophic cerebellar cortex there was a selective involvement of the layers, the Purkinje cells being the most vulnerable, followed in order of susceptibility by the molecular and finally by the granular layer.

The spinal cord revealed noticeable disappearance of nerve cells in the anterior horns. In such areas a few lymphocytes and plasma cells might be present around the small vessels in addition to the many astrocytes and microglial cells.

A comparative examination of the symmetrically cut thalami revealed a diminution of nerve cells in the more severely involved hemisphere. In one case two foci of perivascular infiltration were seen in the pulvinar.

In other regions of the central nervous system neither perivascular infiltrations nor cell nodules were present.
Distribution of Lesions

It is a characteristic feature of the brain in encephalitides that the reactive responses of the glia and the vascular mesenchymal tissue are quantitatively limited, and it is not uncommon for different agents to produce similar morphologic changes. In addition, alterations of nerve cells are frequently non-specific and usually do not assist in differential diagnosis of the encephalitides. Therefore, proper study of an encephalitic process requires consideration not only of the nature of the lesions but also of their distribution in the central nervous system. The distribution of the lesions (perivascular and parenchymal lesions, neuronophagic nodules, and cell nodules) during the early stage and during the height of Teschen disease will now be described.

Comparing the pig brain with that of other mammals, we attempted to locate the important regions of the porcine central nervous system. Figures 16 to 38 present drawings of a few serial sections of the pig brain and cord. The left half of each drawing shows the normal structure with the important regions depicted. The right half is marked with dots to give a composite representation of the lesions occurring in each area.

In the preceding discussion, the regions in the central nervous system described in detail represent, with the exception of the telencephalon, the most involved areas in Teschen disease at its height. The widespread distribution of the lesions at the height of Teschen disease is indicated in Figure 15. The most widespread involvement was present in the spinal cord and invariably in the cerebellum. Next most severely involved were the thalamus, medulla, and pons, followed by the mesencephalon. The nucleus olivaris was markedly involved in the majority of cases. Moderate perivascular infiltrations occurred consistently around the aqueduct.

Selective damage of bulbar and pontine nuclei was not observed; individual differences, however, might occur from case to case. In some animals, for instance, the basal parts of the pons were slightly more involved than the dorsal.

However, the over-all impression gained during study of the medulla and pons was that the dorsal and ventral portions of each were involved to approximately the same degree. To confirm this impression total lesion counts were carried out in the serial sections of the medulla and pons of 8 animals (3 intracerebrally inoculated, 3 orally, and 2 intranasally). These results are given in Table I. Marked variation among individual sections occurred; sometimes the ventral lesions outnumbered the dorsal or vice versa. This variation is indicated in the column maximum ratio in Table I which gives the numerical ratio
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(dorsal/ventral or ventral/dorsal) for the individual section showing the most variation within a single case. When the total lesions occurring in all sections of a single case were considered, however, it was seen that there was no significant difference between dorsal and ventral involvement, at least in the 8 animals studied.

Involved with decreasing severity were the nuclei septi pellucidi; the pallidum and putamen; and, finally, the caudate nucleus and

**Table I**

Relation of Distribution of Lesions in the Ventral and Dorsal Parts of the Medulla and Pons

<table>
<thead>
<tr>
<th>Case number and route of inoculation</th>
<th>Medulla</th>
<th>Pons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of lesions counted</td>
<td>Percentage</td>
</tr>
<tr>
<td>12 Intracerebral</td>
<td>163</td>
<td>52 48</td>
</tr>
<tr>
<td>3 Intracerebral</td>
<td>133</td>
<td>52 48</td>
</tr>
<tr>
<td>18 Intracerebral</td>
<td>203</td>
<td>48 52</td>
</tr>
<tr>
<td>35 Oral</td>
<td>121</td>
<td>46 54</td>
</tr>
<tr>
<td>123 Oral</td>
<td>112</td>
<td>50 50</td>
</tr>
<tr>
<td>117 Oral</td>
<td>225</td>
<td>51 49</td>
</tr>
<tr>
<td>52 Intranasal</td>
<td>179</td>
<td>56 44</td>
</tr>
<tr>
<td>53 Intranasal</td>
<td>116</td>
<td>50 50</td>
</tr>
</tbody>
</table>

*V = ventral.
†D = dorsal.

rhinencephalon. The remainder of the cerebral cortex revealed moderate changes, the base being more involved than the convexity (including the motor cortex). The frontal lobe and the basal temporal gyri were more affected than the parietal lobe. The occipital lobe was occasionally and mildly involved. The ependyma revealed no changes.

The white matter rarely disclosed perivascular infiltrations and cell nodules. Infiltration of the choroid plexus was seen in only one case.

In the incubation period, loose cell nodules and mild perivascular infiltrations were scattered at random in the cerebellum, rhinencephalon, and rarely in the pons and medulla. At that time the spinal cord usually was not involved.

Orally, intranasally, and intracerebrally inoculated animals were
compared with regard to the distribution of the lesions in the central nervous system. Taking into consideration that individual differences may occur from case to case among similarly inoculated animals, no characteristic differences were found in the distribution of the lesions in the early stages or in the midcourse of the disease among the three inoculated groups.

**Comment**

Spielmeyer\textsuperscript{20} classified the encephalitides on the basis of the histologic nature of the inflammatory reaction. Considering the predominantly mesenchymal reaction in general paresis and the almost pure glial inflammatory response in typhus encephalitis as the two extremes of a scale, he called poliomyelitis a glial-mesenchymal inflammation. Similarly a glial-mesenchymal inflammation is seen in Teschen disease. The chief participants in the inflammatory reaction are lymphocytes and microglia. Predominance of polymorphonuclear leukocytes occurs only rarely and for a limited time in the early stages of Teschen disease.

Teschen disease is a non-purulent encephalomyelitis of the gray matter, the involvement of the white matter being rare and minimal. The destruction of nerve cells in some regions of the central nervous system, such as the spinal cord, is very rapid and severe. In other areas, such as the cerebral cortex, definite regressive changes in nerve cells are rarely seen and they seem to bear no definite relationship to either the number or extent of the foci of perivascular infiltration. Our findings are in agreement with those of Kment,\textsuperscript{8} who did not find inclusion bodies; on the other hand Scheuer\textsuperscript{7} reported “many inclusions” in the nerve cells.

Besides the degeneration of the nerve cells and the perivascular infiltrations, the cell nodules are among the characteristic morphologic features of Teschen disease. Although often occurring in close relation to the vessels, they may appear independently. These nodules may be either loosely formed or very compact and large. The former type predominates in the cerebral cortex while the latter occurs more frequently in the cerebellum. Glial cuffs around infiltrated vessels usually do not occur. Scholz\textsuperscript{21} made the same observation in von Economo’s disease. Sometimes there is a moderate, diffuse increase of the glia in the subcortical areas of the attacked cortex. Aside from these findings the white matter contains occasional perivascular infiltrations and, more rarely, cell nodules.

Although the more massive involvement occurs chiefly in the diencephalon, midbrain, cerebellum, medulla, and cord, there is virtually
no part of the brain that is not involved at one time or another. Compared with the severe morphologic manifestations in the regions just mentioned, the pathologic changes in the telencephalon are constant but moderate, revealing quantitative variations from case to case. The rhinencephalon and generally the base of the brain are more involved than the lateral parts and the convexit.

The brain in orally, intranasally, and intracerebrally inoculated animals is involved earlier in the course of the disease than is the spinal cord. This is clearly shown in the early stages of the disease, when fever is the only sign; then one may find, with lesions in the cerebrum and cerebellum, either no changes in the cord or involvement only of the cervical cord, the thoracic and lumbar regions remaining free.

There are differences of opinion among authors concerning the distribution of the lesions in Teschen disease. It has already been mentioned that many have been impressed by the localization of the process in the spinal cord and have emphasized this aspect. In the early literature there is only one report of a case with encephalitic involvement without changes in the cord.\textsuperscript{11} Baumann,\textsuperscript{9} Kment,\textsuperscript{8} and others have reported that, next to the cord, the most severely involved areas are medulla and pons. In the cerebellum a varying leptomenigitis is said to occur.\textsuperscript{8} Traub\textsuperscript{11} stated that the cerebellum and thalamus are less involved than the olfactory bulbs and Ammon's horn and are as severely attacked as the striatum. All authors have found lesions in the striatum and pallidum, but there is disagreement concerning the severity of the involvement. Many have found lesions of moderate or slight degree in the cerebral cortex.

Recently Környey and Elek\textsuperscript{22} found no changes in the striopallidum. Furthermore, they did not seem to be impressed by the moderate cerebral cortical involvement in their cases. Thus they classified Teschen disease with the "focal polioencephalitides with a predilection for the brain stem (Encephalitis epidemica type)."\textsuperscript{23} Our experiences, in examining over 300 pig brains, differ in certain respects from the above statements, as has been pointed out in the preceding description of the lesions. Presentation of our convictions will be further clarified in the subsequent comparison of Teschen disease with other viral encephalitides.

The pathologic findings in several important areas of the central nervous system indicate a certain variability in the morphologic manifestations from region to region. There are, for example, marked and manifold degenerative changes in the nerve cells of the anterior horn. On the other hand, one must search long and hard to find regressive
neuronal forms in the cerebral cortex. In both the cerebellum and the
thalamus nerve cells may undergo total vacuolization, but phagocytosis
and glial reaction are different in the two regions. The morphologic
manifestation appears to depend in some way upon the area involved.

The following can be stated concerning the relationship of "neuronal
damage" to the "glial-mesenchymal reaction" in Teschen disease. Al-
though the gliomesenchymal reaction in some regions is less extensive
than the degeneration of nerve cells, we never observed isolated de-
generation of nerve cells without reaction of the glia or mesenchyma
even in the early stages of the disease. This does not mean, however,
that the two reactions are necessarily and always interdependent, since
perivascular cuffs may be present in areas without neuronal damage
and one can see well preserved nerve cells among lymphocytes, plasma
cells, and microglia, a finding which is known to occur in various en-
cephalitides.

More cells participate in the phagocytosis of nerve cells than appear
necessary from a functional viewpoint. For instance the individual
neuronophagic nodules and "Strauchwerk" formations in the cerebel-
rum are much more cellular than the corresponding formations seen in
non-infectious diseases. Thus it appears that the agent causing the dis-
ese is capable not only of inducing a primary glial-mesenchymal in-
flammatory response, but also of influencing the ultimate form of
neuronophagia and "Strauchwerke."

Meningitis in Teschen disease is not always related and proportional
to cortical damage. Meningeal reaction is a very early sign of the ill-
ness and occurs in the late incubation period either with or without
minimal degeneration of the cortical nerve cells.

Care must be exercised in the interpretation of the findings in the
ganglia since some of the so-called pathologic changes occur normally
in the ganglia of man and animals. It has been reported that lympho-
cytes and mast cells occur under normal conditions in the ganglia of
humans. For example, the inflammatory infiltration described in the
stellate ganglia in causalgia was later found in cases unrelated to
causalgia, such as accidental death. Bodian and Howe and Faber
et al., working with poliomyelitis in monkeys, found changes in the
ganglia in two of three control animals.

In selecting criteria of neuronal degeneration it is well to remember
that the Nissl substance of nerve cells in the ganglia is normally not
distinct and is often dust-like in appearance. There is individual vari-
tion in the number of cells present, and so-called "shrunken" nerve
cells occur normally in ganglia. Neurons showing retraction of the
cytoplasm from the capsule and resembling "celulas fenestradas" (Cajal) also occur normally in the ganglia of the pigs.

The ganglia of many infected animals, especially in the early stages of Teschen disease, reveal mild inflammatory changes which do not differ either qualitatively or quantitatively from those seen in the controls. However, the ganglia of the more severely affected animals often contained more massive inflammatory changes and occasional neuronal changes as well. These latter alterations were never seen in the control animals.

The liquefaction and retraction of altered nerve cells is usually accompanied by proliferation of the capsule cells, neuronophagia occurring very rarely in ganglia. It is emphasized that these two processes are entirely separate.

Among the reports in the literature only Kment\(^8\) mentioned liquefaction and shrinkage of nerve cells in the spinal ganglia as occurring in Teschen disease. In addition, he found infiltration composed of lymphocytes and macrophages. All of these findings were considered by Baumann\(^9\) as non-specific for Teschen disease.

**Correlation of the Clinical Signs with the Anatomical Changes**

In encephalitis as widespread as Teschen disease it is difficult to localize the basis for individual neurologic signs. It cannot be proved, for instance, that the disturbances of coordination and equilibrium are due only to the midbrain involvement\(^22\) or that the tonic convulsions and the opisthotonos are due to the lesions of the brain stem.\(^22\) Since the neurophysiology of the pig is an uncharted field, it is dangerous to make restricted correlations between clinical signs and anatomical lesions. In general terms, however, one may correlate the severe involvement of the cerebellum and basal nuclei with the clinical manifestations of ataxia, forced movement, and tremors. In addition, the relatively late onset of paralysis of the extremities is in accord with the anatomical findings of late involvement of the spinal cord in this disease.

**Comparison of Teschen Disease with Other Viral Encephalitides**

On the basis of a single morphologic feature one may find resemblances among viral encephalitides. The perivascular infiltrates, cell nodules, and generally the glial response are similar in many viral inflammatory processes of the central nervous system, for instance, in Teschen disease, poliomyelitis in man and monkey, and Japanese B encephalitis in man.
Környey and Elek\textsuperscript{22} believed that Teschen disease and von Economo's disease have striking morphologic similarities. In both, the involvement of the brain stem is very marked. However, in von Economo's disease the thalamus, a region of predilection in Teschen disease, is spared of lesions with the exception of a small paraventricular area.\textsuperscript{28} Conversely, the cerebellar cortex, which in Teschen disease is constantly involved, is only "minimally or not at all altered" in epidemic encephalitis.\textsuperscript{28}

Other authors have considered poliomyelitis and Teschen disease to be similar on the basis of changes occurring in the spinal cord. The changes are, indeed, strikingly similar; however, the involvement of the entire cord, and especially of the posterior horns, is more extensive in Teschen disease, and there is not the relative sparing of the thoracic cord that is frequently seen in poliomyelitis. Furthermore, the encephalitic manifestations of the two diseases are quite different. The motor cortex, a region of selective involvement in poliomyelitis, is only slightly altered in Teschen disease and appears to be much less vulnerable than other areas, e.g., cerebellum, thalamus, midbrain, caudate nucleus, and rhinencephalon. More extensively involved than the motor cortex is the base of the brain, as has been mentioned.

The regions rarely if ever affected in poliomyelitis, according to Bodian,\textsuperscript{29} "include primarily the entire cerebral cortex, except for the motor area, the corpus striatum, except occasionally for the globus pallidus, the cerebellar cortex except for the vermis, and the base of the pons." In Teschen disease these regions are constantly affected and their involvement is far more massive than in poliomyelitis. Polymorphonuclear leukocytes, which occur relatively often in the early stages of poliomyelitis, are rarely seen in Teschen disease. It is possible, of course, that they occur, but more transiently than in poliomyelitis.

Wolf published a useful classification of some common viral encephalitides grouped on the basis of the selectively affected regions.\textsuperscript{30} He separated the encephalitides into three groups. In group one, which includes lethargic encephalitis, "one end of the brain, its caudal extremity, the brain stem, suffers most." In group three, including herpes simplex and inclusion encephalitis, "the rostral extremity of the brain, represented by the cerebral cortex, suffers most." The second group is composed chiefly of the arthropod-borne encephalitides. "In these, the lesions are found in all parts of the nervous system, with the brunt of the attack being borne by the basal structure of the brain and by the cerebral cortex."
Of the encephalitides included in group two, the equine encephalitides and St. Louis encephalitis reveal morphologic features entirely absent in Teschen disease; e.g., involvement of both gray and white matter and areas of encephalomalacia.

There are many similarities between the distribution of the lesions seen in Teschen disease and those found in Japanese encephalitis in man. Diencephalon, midbrain, cerebellum, and medulla are markedly affected. Cell nodules are characteristic in both, but in Japanese B, their distribution is more uniform and extensive in the cerebral cortex, especially along the lateral fissure and the upper convex surface of the brain, areas which are less involved in Teschen disease. Leptomeningitis in Japanese B is more striking over the cerebrum and minimal over the cerebellum, whereas the opposite is found in Teschen disease. Zimmerman described circumscribed zones of acute degeneration, pale in appearance and without mesenchymal or glial response, in Japanese B encephalitis. Such degeneration does not occur at all in Teschen disease. Of the viral encephalitides, Japanese B, except for the differences mentioned, bears a close resemblance to Teschen disease.

There are many morphologic similarities between Teschen disease and louping ill, at least in experimental infections of monkeys and pigs. In both diseases, the cerebellum is markedly involved although the microglial reaction of the molecular layer in louping ill of monkeys is less pronounced. In louping ill, involvement of the cerebral cortex and caudate and lenticular nuclei does not show the quantitative differences seen in Teschen disease, nor is the involvement of the diencephalon so constant. In the cord acute necrosis is missing and changes ending in death of nerve cells are uncommon.

When the morphologic features are considered as an entity, Teschen disease is seen to differ from other viral encephalitides.

**SUMMARY**

A study of the pathology of Teschen disease reveals it to be a widespread encephalomyelitis confined almost entirely to the gray matter. The lesions consist of degenerative neuronal changes, perivascular infiltrations, and neuronophagic and cell nodules; the latter may be of loose or compact organization, are often found in relation to vessels, and occur in large number at the height of the disease. Microglial cells are the common elements of neuronophagic and cell nodules. The perivascular infiltrations are composed predominantly of lymphocytes.

The relationship of the neuronal damage to the reaction of glial and
vascular-mesenchymal tissue has been discussed. It was found that the perivascular infiltrations and the glial reaction can occur not only as a secondary response to neuronal degeneration but also as primary phenomena.

Meningitis is one of the early manifestations of Teschen disease; the inflammation of the meninges is very marked in the cerebellum, moderate in the cerebrum, and slight in the spinal cord.

The morphologic manifestations of the disease vary in intensity and quality in different parts of the central nervous system. The distribution of lesions in the early stages and at the height of disease has been discussed. In the fully developed disease the most severely involved areas are in the cerebellum, cord, thalamus, medulla, midbrain, and pons; less severely affected are the caudate nucleus, putamen, and pallidum. The cerebral cortical lesions are moderate and are more prominent in the rhinencephalon than in other parts of the cortex.

The findings in the peripheral ganglia in Teschen disease were studied and critically considered.

The morphologic changes in animals which had recovered from the acute stage of Teschen disease have been described.

Teschen disease has been compared with other viral encephalitides. When the comparison is limited to one or a few morphologic features, similarities to certain of these encephalitides are found. However, when the entirety of morphologic changes, including their quality, quantity, and distribution, is considered, it is not difficult to differentiate this disease from other viral encephalitides and to establish it as a separate disease entity.

We are indebted to Drs. J. Russel Greig and D. R. Wilson of the Moredun Institute, Edinburgh, for making available to us sections and blocks of tissue from pigs which they infected with loping ill virus in 1930.

REFERENCES
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**LEGENDS FOR FIGURES**

**Fig. 1.** Cerebral cortex. Mild meningitis and minimal perivascular infiltration in the first layer of the cortex. × 70.

**Fig. 2.** Anterior horn of spinal cord. The cell body shown exhibits a mild degree of neuronal degeneration. Nissl bodies hazy in outline. Slight hyperchromatism of nucleus. × 600.

**Fig. 3.** Anterior horn of spinal cord. In the perinuclear area and the cell periphery as well as in the nerve cell process, the Nissl substance is altered but still preserved. The hyperchromatism of the nucleus has progressed as compared with Figure 2. Partial chromatolysis is present. × 600.
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Fig. 4. Anterior horn of spinal cord. Almost complete chromatolysis with the nuclear membrane no longer visible. × 600.

Fig. 5. Anterior horn of spinal cord. Central chromatolysis with peripheral vacuolization. × 600.

Fig. 6. Anterior horn of spinal cord. Complete vacuolization with dissolution of the cytoplasm and karyorrhexis. × 530.

Fig. 7. Anterior horn of spinal cord. Hypertrophic, elongated, and twisted microglial cells. × 940.

Fig. 8. Spinal cord. Many neuronophagic nodules and perivascular cuffing. × 50.
Fig. 9. Anterior horn of spinal cord. Marked destruction of neurons. Many neuronophagic nodules. Intensive perivascular infiltration with lymphocytes. $\times 90$.

Fig. 10. Vacuolated Purkinje cells. $\times 440$.

Fig. 11. Cerebellum. (a) Complete destruction of the Purkinje cells with proliferation of the Bergmann glia. (b) Several Purkinje cells still remaining. In the molecular layer a few "Strauchwerke" are present. $\times 85$.

Fig. 12. Cerebellum. Numerous areas of neuronophagia and many cell nodules, especially in the Purkinje layer. Moderate perivascular cuffing. $\times 42$.

Fig. 13. Cerebral cortex. Perivascular infiltration and loose cell nodule. The nerve cells are very well preserved. $\times 60$.

Fig. 14. Cerebellar atrophy. Selective destruction of the layers of the cerebellar cortex with marked gliosis. A moderate meningitis is present. $\times 42$. 
FIG. 15. A composite diagram illustrating the distribution of the lesions (indicated by dots) in the pig brain and medulla.

FIGS. 16 to 38. Figures 16 to 35 represent drawings of transverse sections of the pig brain, Figure 16 being most anterior (frontal lobe) and Figure 35 most posterior (medulla). Figs. 28 and 29. Transverse sections of the occipital lobe. Figs. 30 to 34. Transverse sections of the cerebellum. Fig. 36. Transverse section of the cervical cord. Fig. 37. Transverse section of the thoracic cord. Fig. 38. Transverse section of the lumbar cord. The numbers (1 to 87) on the left side of the drawings indicate the following anatomical regions of the pig brain, while the dots indicate the distribution of lesions: 1. sulcus praesylvius; 2. gyrus sigmoideus posterior; 3. gyrus lateralis; 4. gyrus genualis; 5. gyrus proreus; 6. gyrus coronalis; 7. cavity of the olfactory bulb; 9. attachment of the bulb to the base of the brain; 10. gyrus hippocampi; 11. lateral ventricle; 12. motor cortex; 13. claustrum; 14. nucleus caudatus; 15. undifferentiated matrix cells around the lateral ventricle; 16. putamen; 17. capsula externa; 18. capsula interna; 19. nuclei septi pellucidi; 20. optic nerve; 21. corpus callosum; 22. gyrus rostralis; 23. gyrus forniciatus; 24. gyrus lateralis; 25. sulcus lateralis; 26. gyrus suprasylvius; 27. gyrus suprasylvius anterior; 28. gyrus obitalis; 29. sulcus suprasylvius; 30. third ventricle; 31. chiasma opticum; 32. optic tract; 33. fornix; 34. thalamus; 35. pallidum; 36. nucleus amygdalae; 37. temporal horn of the lateral ventricle; 38. Ammon's horn; 39. fascia dentata; 40. corpora geniculata; 41. corpus quadrigeminiun anticum; 42. substantia grisea centralis; 43. aquaeductus Sylvii; 44. Westfall-Edinger nucleus; 45. nucleus nervi oculomotorii; 46. substantia nigra; 47. nucleus ruber; 48. pes pedunculi cerebri; 49. corpus pineale; 50. formatio reticularis; 51. nucleus ventralis thalami; 52. fourth ventricle; 53. posterior horn of the lateral ventricle; 54. vermis; 55. cerebellar hemisphere; 56. corpus quadrigeminiun posticum; 57. nuclei pontis lateralis, medialis and ventralis; 58. nucleus Gudden; 59. ganglion intermediulare; 60. nucleus dorsalis raphe tegmenti; 61. nucleus ventralis and dorsalis brachii conjunctivi; 62. nucleus nervi trochlearis; 63. nucleus proprius substantiae griseae centralis; 64. nucleus dorsalis, medialis and ventralis lrennisci lateralis; 65. lingula cerebelli; 66. nucleus motorius and sensibilis nervi trigemini; 67. nucleus Bechterew; 68. brachium pontis; 69. flocculus cerebelli; 70. radix mesencephalica nervi trigemini; 71. nucleus ventralis raphe tegmenti; 72. nucleus ventralis formatio reticularis; 73. formatio reticularis lateralis; 74. nucleus lateralis formatio reticularis; 75. nuclei trapezoidi; 76. nucleus paralivaris; 77. nucleus olivaris inferior; 78. nucleus funiculi lateralis; 79. substantia gelatinosa; 80. nucleus ambiguus inferior; 81. nucleus nervi VII; 82. nuclei nervi XI; 83. cellulae zonales; 84. cellulae terminales; 85. cellulae Gierke; 86. nucleus Goll; 87. nucleus Burdach.
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Figs. 30 to 38. The numbers refer to anatomical regions as listed on page 592; the dots designate the distribution of lesions as identified.

Figs. 30 to 34. Transverse sections of the cerebellum.

Fig. 35. Most posterior transverse section of brain (medulla).

Fig. 36. Transverse section of the cervical cord.

Fig. 37. Transverse section of the thoracic cord.

Fig. 38. Transverse section of the lumbar cord.