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Pathology of Enzootic Ataxia of Lambs

By

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With 10 Figures in the Text

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The interest of an intensive study of "Swayback" for the neuropathology of demyelinating disease, rests on two facts:

1.) Enzootic ataxia or swayback has been related to Schilder's disease — which is of course closely related to disseminated sclerosis — because of the fact that one sometimes sees in the ataxia of lambs a gelatinous appearance of the white matter (INNES 1939). To be more precise it is the infantile form of Schilder's disease that has been most frequently cited in this regard (MACKAY 1940; WINKELMAN and MOORE 1942; INNES 1943) but INNES and SAUNDERS have more recently (1957) stated that "this does not however imply any causal relationship".

2.) Swayback would appear to be a demyelinating disease forming from the pathogenetic point of view part of a generalized disorder — which may possibly also be local — involving a disorder of copper metabolism (BENNETS 1937).

It is an attempt to co-ordinate these *morphological analogies* and the *disorders of metabolism* involved which forms the starting point of the histopathological and biochemical research that we have undertaken as a team in the last five years.

In this work we shall only discuss the histopathological findings.

Our observations concerning the animals originate in regions as different as those of Thessalonica (Greece) and Reykjavik (Iceland). This is not without interest nor is it unintentional. One must ask oneself wheter there are not differences between the ataxia of lambs observed in England and in Greece and those described in South Africa, in New Zealand and in Australia. Geographical variations can perhaps explain why different observers have published series in which the frequencies and the qualities of the lesions have been very variable. These variations are of such a degree that one sometimes asks oneself whether the descriptions do really correspond to identical morbid entities.

The first lesions seen by BENNET (1932) were described as degenerations of fibres in the thoraco-lumbar spinal cord and in the sciatic and femoral nerves. Some cases with more protracted evolution showed a sclerosis of the spinal cord. These spinal cord lesions were localised, according to STEWART (1932), in the spinocerebellar tracts and in the column of Goll and were accompanied by anomalies of the cells of the column of Clarke in the thoracic cord.

The cerebral lesions were described for the first time by INNES and SHEARER (1939). They compared the early cerebral lesions with those of diffuse sclerosis. In early cases, the cavitation might sometimes be absent and replaced by a bilateral gelatinous degeneration of the white matter. "In a series of cases once one observed all gradations, extending from this severe type with symmetrical foci demyelination often present, up to those which showed no gross changes." The demyelination was of rapid evolution, the axons being affected at the same time as the myelin; there were no fatty products of degeneration nor perivascular reaction, no compound granular corpuscules, no histological evidence of inflammatory reaction, the nerve cells were intact except for those of the red nucleus where one observed a chromatolysis. The cavities were enclosed by zones of glial fibres, a gliosis that could be demonstrated by the use of special methods but "not as pronounced as in the analogous human diseases". There was in addition a degeneration of the motor pathways in the spinal cord. "Two well defined tracts are affected by a descending degeneration: fibres which are present in the anterior column near the median fissure and a bundle forming a central group in the lateral column near the head of the posterior horn ... They probably represent a combination of pyramidal and rubrospinal degeneration."

The cerebral lesion described by INNES and SHEARER were confirmed by BENNETS and BECK (1942) who also found the degeneration of the myelin of the cerebellar pathways in the thoraco-lumbar cord but without a strict systematization. This degeneration of the direct cerebellar tracts and the zone of Lissauer was found in 56 out of 57 cases (BENNETTS and BECK 1942), the dorsal and ventral roots showing frequently degenerated nerve fibres. There were no lesions in the neurones. In 13 out of 22 cases studied with the Marchi method there were lesions of the sciatic and femoral nerves. There were no constant lesions in the brain in 11 cases subjected to post-mortem examination.

MCDONALD (1942) amongst 22 cases studied did not find a single example with cerebral lesions. The others showed spinal cord lesions with degenerative lesions, not only of the neurones of the red nucleus but of the giant multipolar cells of the brain stem and the spinal cord.

In a review (1943) INNES made the following point as to the anatomical problem: "although the pathology may have appeared to permit a study and a classification, there are still numerous points which remain debatable and there are even those for which we are quite unable at present to advance an explanation. For example, we do not completely understand the relation between the cerebral lesions, the degeneration of the motor pathways in the spinal cord and the neuronal lesion in the red nucleus ... from the pathological findings one could conclude that the lesions arise at an advanced stage in the pregnancy and that the causal agent only affects the lamb during intra-uterine life."

INNES and SAUNDERS returned to this theme again in 1957: "The pathology of Swayback is represented by a form of symmetrical cerebral demyelination reaching variable degrees in different cases. In the very benign forms only histological lesions can be demonstrated, but in others one sees with the naked eye zones of gelatinous degeneration reaching diffuse bilateral softening and microcavitations, while in the more severe cases the white matter of the cerebral hemispheres is liquefied and transformed into cavities, recalling the porencephalic brain, but the disease is not a true porencephaly. The grey matter is relatively spared, inflammatory cells and inclusions are not present. Chromatolytic changes are seen in the cells of the red nucleus. There is almost always a secondary degeneration in the spinal cord affecting the upper pyramidal pathways and the rubrospinal (motor) tracts."

BARLOW (1958), with a large personally studied material, noted the absence of lesions of the cerebral myelin in 62% of cases. He observed in 97.5% of cases aged less than 2 weeks, changes of a chromatolytic type extending up to a necrosis in the large neurones of the brain stem and in the anterior horns, lesions which were confirmed by Holme's technique for demonstrating the neurofibrils. Marchi-positive fibres were present in the younger cases, in the brain stem and in the spinal cord, and in the region of the dorso-lateral fasciculi and the sulco-marginal fibres, but he found similar lesions in this situation in normal animals aged less than 10 days. The presence of glial fibrils at the borders of the cavities was confirmed by BARLOW (1958) but without intense glial proliferation. In two cases, he noted the presence of large quantities of compound granular corpuscles around the vessels in the lesions extending into the cortex. In the foetal nervous system of controls he observed in the cortical neurones

a stippled appearance of the cytoplasm with spaces formed by retraction and, where demyelination was still in progress, a gelatinous appearance with the same quantities of sudanophil material around the vessels as seen in the affected aninals.

How can these discrepancies be reconciled?

Is it possible that some authors have studied congenital forms and others delayed forms? Is it possible that there are predisposing causes such as the coexistence of anaemia, such as has been reported in the Australian and New Zealand observations?

The *clinical picture* is a uniform one and we shall only recall it here in order to justify certain precautions we have taken in the choice of our material.

This disease of lambs born to healthy mothers; irrespective of the race, appears at birth or in the first weeks. When there are multiple births one or several lambs can be affected in variable degrees. According to the severity of the ataxia, the disease progresses towards a fatal conclusion or, if it is one of the lighter forms, the animal adapts itself, is quasi-completely cured and may give birth in its turn to healthy offspring. The severest forms are represented by still-born lambs or those incapable of any movement or of being able to suckle and which may die within 24 hours. One can keep them alive only by forced feeding. The less severe forms have a jerky gait, spastic, with falls: the inco-ordination is particularly marked in the posterior limbs, but can equally well affect the anterior limbs. The cry is normal. There may be blindness. There are often secondary infections which bring about death.

In regions where the disease is recognised, the diagnosis does not prevent any difficulties if the veterinary surgeon sees the animal himself. A certain number of cases are however brought to him from a great distance (as is the case of Thessalonica) either dead or in an agonal state. The diagnosis must then be based on the history given by the owner or the shepherd.

In every series of "Swayback" lambs studied there are one or two control lambs which are certainly free from the disease. The Greek series comprised 25 cases (with 6 control and 3 doubtful cases)—the Icelandic series 10 cases (1 control and three dubious cases).

The *doubtful cases* have been eliminated for the following reasons.

In the Greek series the first case S. 30/57 (IB 38—39/58) died from bronchopneumonia: a light gliosis in the axis of F2—Fa and of the angular parietal convolution with perhaps a slight diminution in the myelin staining in these areas. In the hippocampus and the caudate nucleus some perivascular infiltrations may be due to the terminal bronchopneumonia.

The second case S 26/56 (IB 36—37/58) was taken from a flock where there had been cases of ataxia and from a mother treated by NaCl. Cachetic lamb without marked neurological manifestations. Killed on the 5th day. Increase in the glia in perivenous trails in the parietal white matter with stasis. This case is a doubtful one. We have eliminated it though one cannot altogether exclude the possibility that it is an early case.

The third case S 34/54 (IB 40/58) was born to a treated mother. Cachectic without neurological manifestations. Sacrificed on the 5th day. Negative from the point of view of cerebral lesions.

In the Icelandic series two cases (IB 60/59 and 61/59) do not show the typical picture. The anatomical study confirmed in the first case the absence of lesions and the presence of a very discrete meningitis in the anterior region of the spinal cord and the lateral fossa and the lateral groove of the brain stem. In the second case there were no lesions. A third lamb which was clinically doubtful (IB 65/59) concerns a disease which we shall describe separately.

We call *control* lambs belonging to the same family, living under the same conditions of climate and of nutrition and killed at our request: there were seven in all.

In the Greek series, the first control (S 37/57-IB 55/58) was born to a mother who had already given birth to ataxic lambs. Normally developed, it was sacrificed on the 5th day: increase in perineuronal neuroglia in the anterolateral groups and even in the intermediate

groups of the anterior horns and spinal cord. Another control (S 25-IB 94/59) showed a lymphocytic meningitis; a third (S 21/IB 90/59) a light gliosis of the dentate nucleus.

The only Icelandic control (lamb II-IB 69/59) showed a discrete lymphocytic meningitis.

As regards the 7 lambs said to be controls there are then 4 which are not normal from the neuropathological point of view. We have constantly referred to the three remaining controls in the study of the ataxic cases and we will recall later what should be considered as normal for a lamb of this age and what should be discarded as a possible lesion of Swayback.

For some pathologists, the cavitation of the hemispheres, so well shown by INNES and SHEARER, remains the diagnostic lesion. This is a mistake if only from the point of view of the relative rarity of this naked eye cavitation in some series which have been published before us and also in our own cases.

In the Greek series, the cavitation was present in only 4 out of 16 cases, in the Icelandic series in one case in 6 making in all 5 cases out of 22.

It is however rash to compare "Swayback" to Schilder's disease because of the relative rarity of the gross cavitation. It is this that INNES has postulated when he reported that "in the early cases the characteristic cavitation can be lacking and be replaced by a bilateral gelatinous degeneration of the white matter recalling Schilder's disease" (1939) — and, in the same text, he adds that "one sees all gradations from a severe type with symmetrical foci often present, up to cases which do not show any gross changes".

The cavitation and the gelatinous transformation are to a certain extent, even for authors who first studied the disease, optional lesions.

Let us note in passing that the spongy or reticulated transformation of the white matter is not the hall mark of Schilder's disease since one sees it also in the subacute sclerosing leucoencephalitis (THIRY, RADERMECKER and VAN BOGAERT 1956), the leucodystrophies etc. . . Let us emphasize on the other hand that the "pseudo-hydrocephalic" cavitation so typical of Swayback almost never occurs so extensively in Schilder's disease but does indeed in the very severe porencephalies of the infantile encephalopathies.

In the same description of INNES there were already a series of characteristics by which Swayback might be differentiated from diffuse sclerosis of the Schilder type. These are: the sharp demarcation of the marginal and intrafocal glial fibrous reaction, the rarity of sudanophil compound granular corpuscles (apart from a few compound granular corpuscles within the adventitia) and the absence of even symptomatic perivascular reaction.

One must therefore find other criteria for the diagnostic histopathology of Swayback.

We have sought afresh the *muscular lesions* in 9 cases in the Iceland series. In 5, there was a diffuse increase in the sarcolemmal nuclei without lesions of the muscle fibres. In 4, the muscle showed no special changes.

An increase in pale nuclei with increase in the pericapillary and intermysial lymphocytes was marked in one case (Lamb 7-IB 65/59) but in this case it was not an example Swayback but indeed of a necrotising meningoencephalitis of a poorly defined type which we will publish separately.

These features in the muscle may possibly be in relation to the age of the animal (excepting case 7). The 5 cases where slight changes were observed did not differ noticeably in age from those where they were absent. Perhaps there may be at any given age individual differences in the degree of maturation of the musculature.

Lesions of the *peripheral nerves* have been reported with great frequency by certain authors (20—30% in the series of BENNETS and BECK) while others only reported more than from time to time a Marchi-positive fibre.

The Schwann cells, in some of our cases, were a little more numerous than one would have expected but this is without significance since the appearances of the myelin in the same cases does not show any special abnormalities. We have noticed also in some nerve bundles a very slight increase in the density of the Schwann cells but these differences may simply be an expression of the variation in the rapidity of myelination of some bundles.

As far as the *posterior root ganglion* is concerned we have not sufficient controls to be able to express an opinion: we would be tempted to make in this regard the same remark that we will make later in regard to groups of neurones in the anterior horn and the intermedio-lateral zone.

The lesions of the *spinal cord* were present in almost 100% of the cases of BENNETS and BECK (1942) in the form of foci of degeneration of the long tracts although BARLOW (1958) considered them almost as artefacts. As for the anterior horns, we have also observed in controls an increase in the satellite neuroglia of the nerve cells of the anterior horn and the intermedio-lateral zone with a slight increase in the volume of the cell body of the neurone. In none of these cases, was there an increase in fat vacuoles or changes in the neurofibrillar network. These appearances are at the limit of the normal. Between these paranormal appearances and the frank lesions which we will now describe there is an infinity of intermediary forms upon which it is impossible to venture an interpretation. One can observe in this way an increase in the glial cells in the anterior and lateral columns in some controls, associated with a poor myelin staining. The difference in affinity of the two columns for the haematoxylin stain appears to us to be a common place in new born lambs. We would share the reservations of BARLOW (1958) who believed that certain Marchi-positive appearances in the secondarily degenerated tracts are artefacts and would agree that "the study of the central nervous system of normal lambs of the equivalent age with the same standard techniques shows an analogous distribution of Marchi positive fibres", but these Marchi positive fibres were seen by BARLOW himself also, in the dorso-lateral columns and the sulcomarginal and septomarginal fibres.

Having made these reservations, there are without any doubt cases with an abnormal gliosis accompanied by discrete cellular lesions in the anterior horns of the spinal cord and in the nerve cells of the intermediate zone. In some cases, there is even a rarefaction of the ganglion cells. This can be seen in a survey view of the thoraco-cervical region of the spinal cord of lamb S. 10 (IB 67/58) (Fig. 1). This same preparation shows a cellular gliosis of the anterior and lateral columns of the Lissauer zone in contrast to the posterior columns and they correspond in the myelin section to a pale zone.

This same appearance of the nerve cells is seen throughout the brain stem and in the red nuclei. This appearance is not characteristic, it probably represents early neuronal reaction. One never finds cellular reactions comparable with those in Fig. 1 nor of incontestable neuronophagia. In a single case a filamentous necrosis (S 3-IB 85/57) has been demonstrated. We do not know whether we are not here dealing with a lesion of different type. In no case did we see secondary degeneration nor an undoubted and primary involvement of the spinal tracts. One may see a discrete neuronal change with some rarefaction in certain cerebellar folia.

As to the significance of the diffuse and slight neuronal lesions of the cerebro-cerebello-spinal axis in relation to those of the telencephalon, histology can merely state that they appear to be arranged in columns and regard them, in the absence of proof to the contrary, as depending in the same way on a still unknown pathogenic factor.

An as great caution is required in the interpretation of the appearances of the *cerebellar central grey nuclei* and particularly of the dentate nucleus and *red nucleus* because, here also, one observes in controls a certain swelling of the nerve cell body with chromatolysis and a discrete perineuronal gliosis. In one of our controls, one found particularly at the margins of the glial and neuronal reactions of the dentate nucleus an increase in the subpial glia of the cerebellar folia and over the cerebral convexity (IB 69/59 of the Icelandic series). As this animal showed a very slight lymphocytic meningitis this lesion may be a result of this disease.

On the other hand, one can see in an undoubted control (IB 90/59 of the Greek series) a gliosis of myelination in the centre of the digitate white matter of a convolution. We have

not observed any free products of fatty degeneration or of intracellular fat. BARLOW (1958) seems to have seen them when he wrote "comparable amounts (relatively small) of lipoid are present in animals not showing lesions, in very young animals and in the foetus where myelination is in progress and (this) is an argument in favour of the theory that the cerebral lesion is rather due to a myelin aplasia than to a demyelination", a concept put forward by INNES but which was rejected and to which we will return later.

The presence of this gliosis of myelination demands therefore great caution in the interpretation of the axial lesions of the brain which we now discuss.

The *cortex* is not intact. It was systematically studied in the Greek series, the frontal region was affected in five cases, in two of them severely. The parieto-angular region was

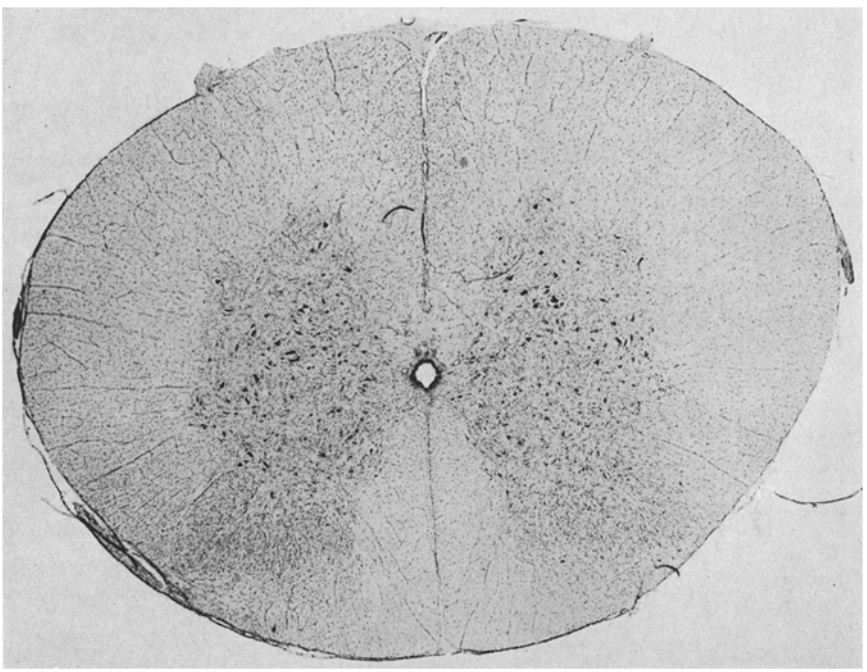


Fig. 1. Survey view of a cytological section of the spinal cord at the junction between the cervical and thoracic regions; rarefaction of the radicular cells of the anterior horn with gliosis—increase in the cellular glia in the anterolateral columns and the zones of Lissauer—(Lamb S 10-IB 67/58) (paraffin, cresyl violet) (× 20)

affected in four cases, and in two of them very severely; the temporal region in five cases, in two very severely, and in two with an average severity. The occipital region was affected in one case with an average severity.

The necrotic cortical lesions are still less than those of the white matter. They are an extension of the latter. In a very large number of foci, the necrosis stops in effect at the subcortical fibres and the characteristic picture is that of Fig. 2 where one sees the process with well established but early disorganisation, but the cortex can also be attenuated by softening as a result of a laminar degeneration (Fig. 3). It may be affected almost in its totality: there remain no more cells in layers II—III and one sees that the necrotic process has already commenced.

The lesions of the white matter show an entire series of graduation. The early lesion (lamb S 2x-IB 84/57) shows itself as a diffuse increase in the neuroglia in the form of a very loose net-work of oligo-microglia with, sometimes, a light pericapillary reaction (Fig. 4). To a more or less advanced degree oligodendroglia and macroglia are added to the bands of microglial cells in trails. At the same time the vessels appear more dilated and in their neighbourhood

glial cells aggregate (lamb S 4-IB 32/58). At a more advanced stage the ground substance becomes granular, then reticulated until it appears as a small cavity (lamb 6-IB 87/57). Capillaries are sometimes surrounded by a sleeve showing endothelial cells and with a dark nucleus accompanied sometimes by a few lymphocytic cells. In the myelin sections all that

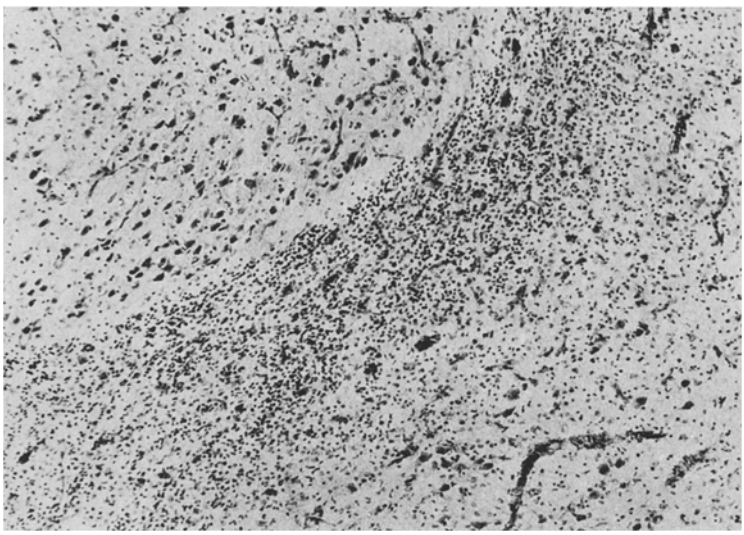


Fig. 2. Typical appearance of a subcortical necrosis revealed in fully developed early stage of transport, the cortex is intact (Lamb S. 7-IB 88/57) (frozen section, cresyl violet) (× 240)

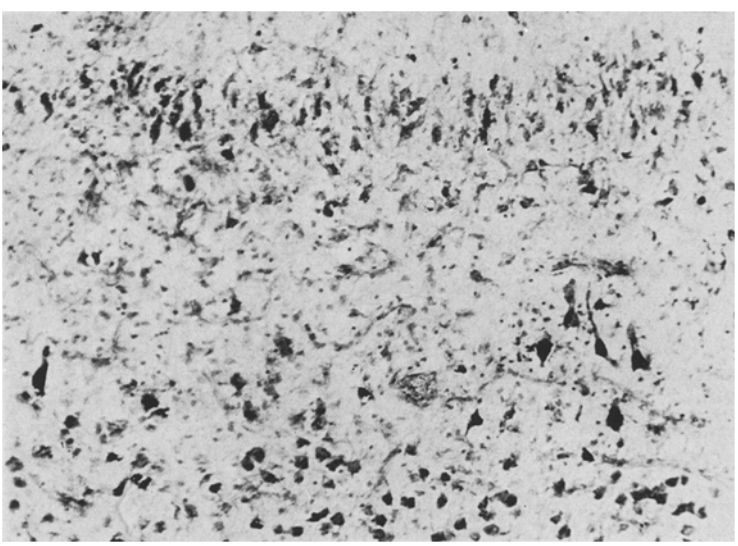


Fig. 3. Laminar necrosis in the IIIrd layer (as Fig. 2) (× 300)

one sees is that the myelin is greyer than usual in the axis of certain convolutions (Fig. 5). There is a commencement of rarefaction of myelin and one finds neither the fatty products of degeneration nor compound granular corpuscules except in isolation as a group of cells in one or other adventitial space.

At a more advanced stage the glial infiltration is no longer apparent: it is necessary to compare sections taken at the same level but treated by different methods. (Fig. 6) (lamb

S 7-IB 88/57) shows three consecutive frozen sections: the first stained with Cresyl violet (Fig. 6), the second with Scharlach R (Fig. 6), the third by a myelin stain (Abb. 6).

In the cytological section one sees the spongy appearences in the peripheral part of the digitate white matter; at the base of this one sees a light cellular infiltration. Over the dome and along the two sides of the convolution, the cortex is rarefied in its layers II to IV. Compare

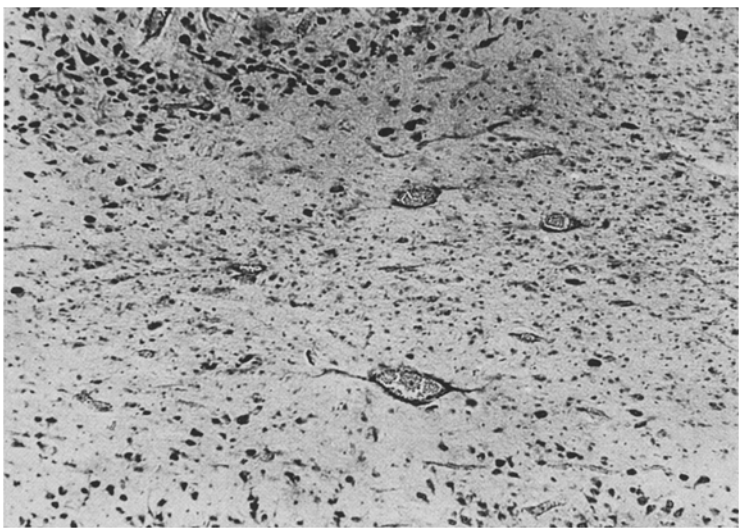


Fig. 4. Early lesion showing venous stasis, the appearance is as of glial cells disseminated in the centre of the white matter sometimes surrounded by a small zone of oedema (Lamb S 7-IB 88/57) (frozen section, cresyl violet (× 240)

its structure with that of the right convolution is unaffected. In the section stained with Scharlach R, the entire cortex and white matter of the dome, and the left side of the convolution are covered by fatty products of degeneration and compound granular corpuscles which continue in the tissue corresponding to the spongy white matter in the depths of the sulcus. The myelin section shows a persistance of fibres in the white matter of the left convolution but a marked myelin rarefaction in the white matter of the median convolution and still more in the subjacent white matter of the centrum semiovale. The differences in density of myelin from one area to another are still more marked in Fig. 7 which is taken from the same case: one finds all degrees of the lesion from simple demyelination (on the right) up to the commencement of a fissural transformation in the centre of the illustration and up to cystic degeneration (on the left).

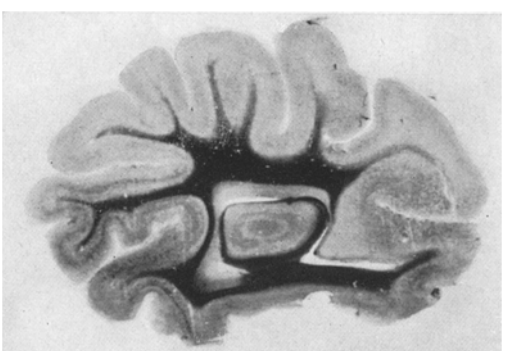
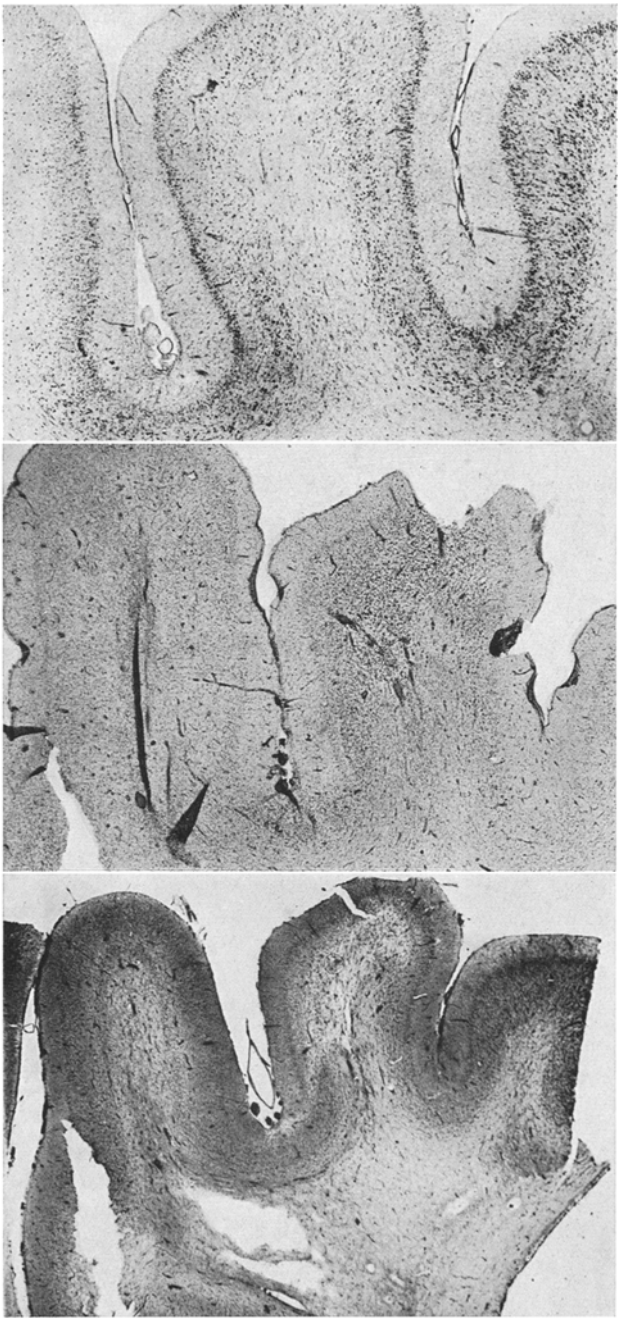


Fig. 5. The demyelination commences in the form of a poor impregnation of the digitate white matter of several convolutions in their most peripheral parts. Compare here the inferior and the lower convolution of the illustration with the two convolutions on the right in the upper part of the photograph (Lamb S 6-IB 87/57) (frozen section, Spielmeyer) (× 5)

The process evolves in the same way in an isolated rounded lesion such as that of the pallidum which one sees in the same case. Two phases of myelin degeneration (Fig. 8) require comment. The fatty products of degeneration can be still dispersed or taken up by compound granular corpuscles and taken towards the adventitial spaces. As to the final state of the axons, Fig. 9 immediately makes this clear to us. By progressive



confluence of all these foci, the centre of the hemisphere ends by being transformed into a large cystic cavity: the hemisphere is no more than a vesicle (Fig. 10). Against the deep surface of the cortex the remains of the white matter forms a thin layer as one sees with cystic tumours.

The degeneration of the white matter of the hemispheres has then nothing of the appearance of a systematic process but develops itself by confluence of zones of spongy necrosis running together and able to penetrate or appear in the cortex and in the central grey nuclei to the same extent as in the white matter.

The transformation and the elimination of myelin debris evolves according to the classical manner, as is shown by histochemical methods. There is scarcely even a slight glial organisation and there is no mesenchymal organisation.

Fig. 6 a—c. The same region is here studied with frozen sections at the same magnification (× 35) by three techniques: a in the cytological section: spongy appearance of the digitate white matter, cortical rarefaction, slight gliosis on the lower left part of the digitate white matter of the median convolution; that on the right has its normal structure (Lamb S 7-IB 88/57) (cresyl violet). b in the section stained with Scharlach R: compound granular corpuscles are seen in the cortex in the spongy zone of the white matter (Scharlach R). c in the myelin section: very intense pallor of the digitate white matter of the median convolution and of the white matter of the centrum semi-ovale (Spielmeyer)

The lesions therefore are of two types:

1. Lesions of focal necrosis formed by the confluence of the vast demyelinated cystic zones occurring with a predilection for the parietal temporal white matter,

sometimes in the cortex of the central grey nuclei, very exceptionally in the spinal tracts (this last point is not quite certain).

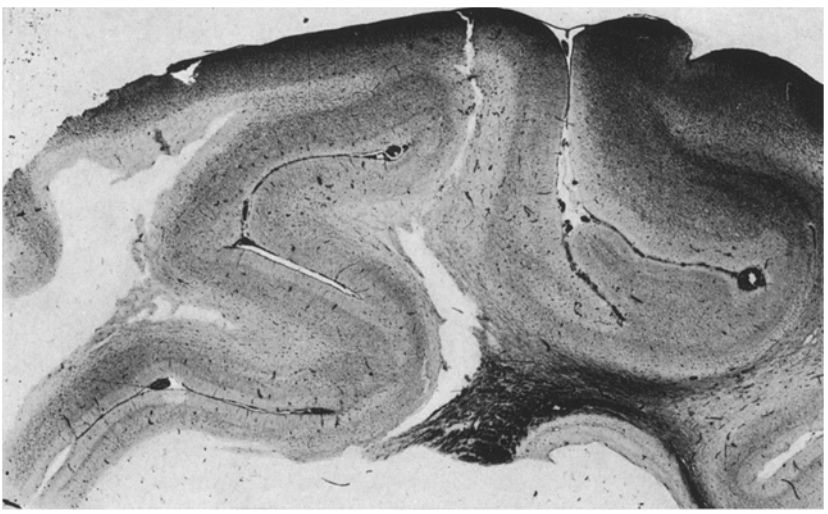


Fig. 7. Survey view of a hemisphere from the same case: one can see in the white matter of the corona radiata a normal myelination—on the right the commencement of demyelination which becomes more and more marked the nearer one approaches the left border of the photograph. Here the myelin has disappeared: there is a cavity. (frozen section, Spielmeyer × 10)

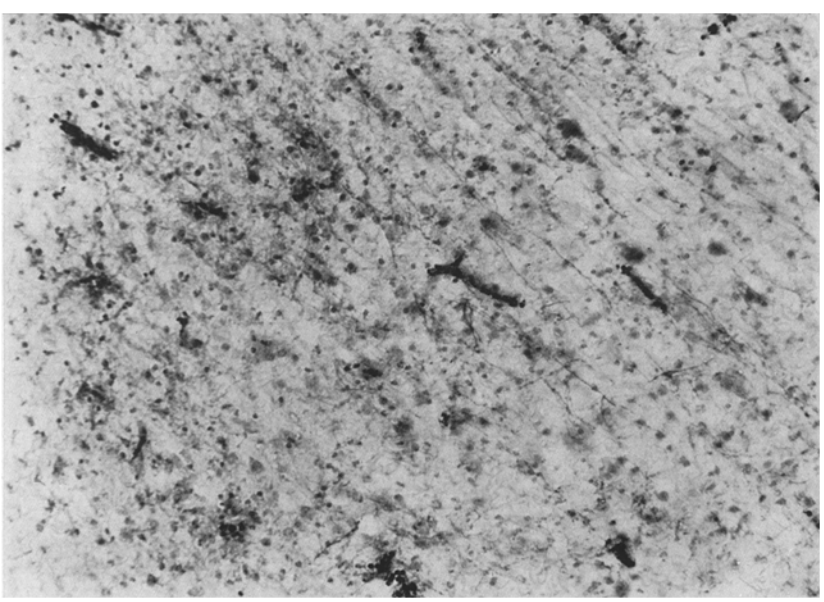


Fig. 8. Same case. At a more advanced stage the myelin has disappeared: there is still a suspicion of the presence of axons, the vessels are visible, their red cells have taken the stain; around the vessels there remain haematoxylinophilic debris (× 300)

2. Cellular changes sometimes of the vacuolar type, sometimes with obliteration of the protoplasmic structures with increase in peri- and intraneuronal glial cells of the anterior root groups of the spinal cord, in the intermediary substance

of these, the red nuclei, vestibular and dentate nuclei, the posterior quadrigeminal bodies, the peri-ventricular magnocellular groups of the brain stem, the nuclei of the raphé and perhaps in the spinal ganglia.

The *intensity* of these two series of lesions varies from one case to another.

Because of the observations made in our control lambs it is necessary to set on one side the following changes.

1. Increase in the light or dark cells of the sarcolemma, of the muscle fibres and the cells of Schwann.

2. Ballooning with pallor of the neurones of the anterior horns, of the dentate nucleus, of the large cells of the brain stem, and the red nucleus.

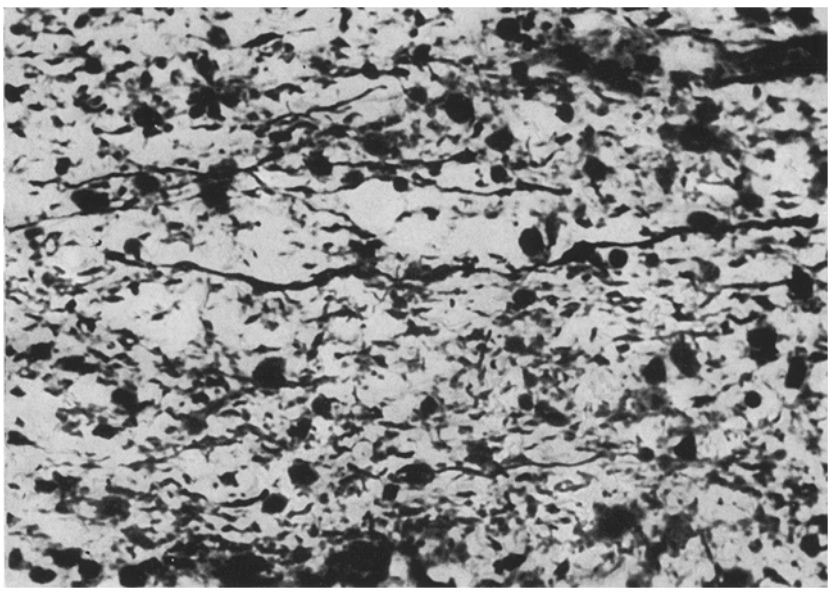


Fig. 9. Same case: nodular and fragmented appearance of axons (frozen technique of Bielschowsky-Reumont) (×300)

3. Numerical increase for the glia either perineuronal or interneuronal in the above mentioned positions.

4. A numerical increase in the glia in the digitate white matter of the cerebral convolutions.

With all due regard to these reservations, one can retain provisionally the following conclusions:

1. The *muscle*, the *nerves*, the *posterior root ganglia*, the *spinal tracts* show in only 2 of our 22 cases undoubted lesions.

2. The *cellular changes* are present in almost half of our cases in the form of cytoplasmic vacuolation with increase in the size of the cell, obliteration of the Nissl substance, increase in vacuoles (this change is rarer). These changes are seen particularly in the large neurones (anterior horn cells, reticular nuclei, vestibular nuclei, dentate nuclei, red nucleus, inferior quadrigeminal bodies, magnocellular nucleus, and periventricular nucleus of the raphé).

We have not in any of our cases dared to face on the presence of these changes alone, the diagnosis of enzootic ataxia.

3. In none of our controls of lambs that have died from some neurological affection differing from the ataxia, have we found the cavitation which was so strongly stressed by INNES and SHEARER. This *macroscopic cavitation* was un-

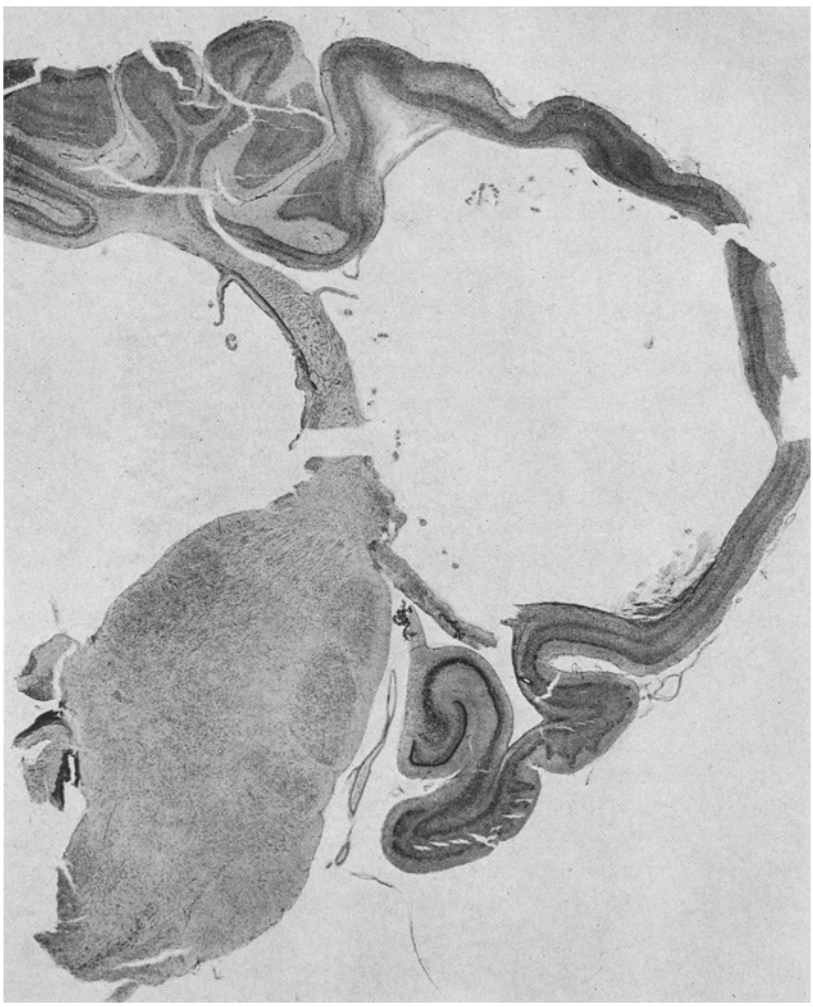


Fig. 10. Survey view of a hemisphere entirely transformed into a cystic cavity: one sees above a zone undergoing liquefaction (Lamb S 10-IB 67/58) (Paraffin, cresyl violet) (× 20)

fortunately only found in five out of twenty-two cases—and a typical *microscopical cavitation* was only seen in two out of the twenty-two cases.

The diagnostic criteria of the ataxic disease in its cavitatory or precavitatory form can then only be postulated in seven out of twenty-two cases, where the clinical diagnosis had been made.

In this series of twenty-two cases we retain however apart from the seven cases mentioned above four cases with a probable but not certain histopathological

diagnosis. *There remained then eleven cases—i.e. exactly half the lambs where the clinical diagnosis had been postulated—which are negative from the point of view of their cerebral histopathology.*

We may ask ourselves whether the structure of the pathological process in lambs justifies a comparison with demyelinating disease in men.

The disease in the lamb commences where the gliosis of myelination is most dense. In this region one sees first a vasodilatation then little by little a granular transformation, finally a reticulation of ground substance of the parenchyma as if it had taken up a hydrophilic or aqueous substance. The neuroglia swells, the myelin stains poorly. The centre of the zone undergoes a fissuring. The fissures round themselves off, then become confluent with other cavities forming finally a single cavity occupying the entire white matter.

Stains for fat show in the first phase a diffuse disintegration, and in the second an accumulation of perivascular sudanophil compound granular corpuscles. Histochemical analysis does not show anything more than simple katabolism.

The affection then shows itself only as a process of primary demyelination.

The changes which affect the myelin affect also the neuroglia which do not show much change at any rate at the commencement. The mesenchyma shows no reaction. Possibly the duration of survival is too short to enable us to see under our eyes a gliomesodermal organisation and it is perhaps especially important to take into account the age of the animal.

Diffuse lesions of the cerebrospinal axis showed themselves also as trophic changes in the neurone with a minimal glial reaction, without marked gliofibrillar organisation and without any mesenchymal organisation at all.

The axial polycystic process suggests a metabolic disorder affecting the nervous parenchyma in its entirety and not only in its myelin structure. It is affected by the status spongiosus but this state is not grafted on to a primary demyelinating process.

The disorder commences and shows itself particularly in those axial regions where the myelination commences. It can localise itself in other areas but the exceptional involvement of the grey matter (pallidum, cortex), at a distance from the typical areas, are perhaps in part a result of functional vascular disorders grafting themselves upon the principle disturbance. From the histochemical point of view there is no evidence of any abnormality whatever in the breakdown of fat.

From the histological point of view, there is no evidence that the brains of these lambs are malformed or retarded in their maturation.

We have no arguments which permit us to suggest that the pathological process has commenced before birth but congenital observations are rather in favour of this concept.

These findings compared with those that we see to-day in the human demyelinating diseases, either of the allergic type or multilocular type, it is clear that enzootic ataxia has nothing in common with these and that one has wished to compare them as an excessive extrapolation.

It is necessary to discuss whether the enzootic ataxia or Swayback has any relation to other diseases described recently in lambs in Great Britain.

A very important problem is that of the relations between Swayback and the congenital hypomyelogenesis of sheep described in April 1959 by MARKSON, TERLECKI, SHAND, SELLER and WOODS. Under this name these authors have published several observations on a congenital disease revealed by tremor, choreiform movements, ataxia and sometimes abnormal movements of the head. Their neuropathological study concerns six cases originating in three different endemic areas. The disease is characterised by normal development and continued integrity of the nerve fibres associated with a bilateral and symmetrical deficiency in the myelination, a deficiency which is marked if not complete in the cerebrum, the mesencephalon and the cerebellum, and this in the absence of any degeneration and any significant tissue reaction. As the ovine myelination is complete in the foetus at the 140th day, it appears to the authors difficult to postulate that one is here concerned with the persistence of a foetal state. Besides, the drawings of the absence of myelination are variable in the six cases and none of these drawings correspond to the foetal type. They add in addition that there is a disorder in the systematisation of the myelination and the improvement of the surviving lambs could make one think of a completion of myelination. At the same time this was not complete in two older lambs that were examined and it is probable that these lambs which by improving their nutrition can survive are able to adapt themselves to the original state of myelin insufficiency.

The same question arises in relation to the relation between Swayback and the Border Disease or "B" Disease described by HUGHES and KERSHAW in 1959 in species of lambs observed in the border land between England and Wales during about 10 years with a variable incidence from farm to farm and from year to year. This disease seems at the same time to be increasing in frequency. It shows itself by a modification of the wool in length, in quality and in colour. The coat of the diseased animals is more curly, often black on the posterior surface of the neck; the skin itself is uniformally darker or darker in patches. The affected animal is smaller, grows more slowly, and has more delicate bones. The gait is clumsy and feeble, there may be a tremor especially in the posterior half in the standing position often rendering walking impossible; on the other hand in these animals suckling can be difficult for the same reason. The lamb may be normal at birth or simply show slight changes in its wool. Many lambs die in the first weeks of life. At autopsy there is no characteristic visceral lesion, but often a loss of skeletal fat and sometimes changes of a dystrophic nature in the muscles. What is most striking is a deficiency in the myelin throughout the entire nervous system but especially in the spinal cord. The authors are not sure whether it is a demyelination or a deficiency in the formation of myelin but the axons of the unmyelinated fibres appear normal.

The shepherds observe that animals affected by the disease and in whom the affection of the fleece is the dominant feature are healthy at birth, that they stand and suckle earlier than normal lambs, are larger and with better bony development. In spite of this vigorous appearance a small number among them gain sufficiently in weight to be sent to the butcher. The affected lambs were not used for reproduction. However in cases where this has occurred, some of the ewes give birth to affected lambs.

The authors add that if it is really a demyelination the disease is close to Swayback but if it is simply an incomplete form of defect in myelination the analogy is superficial.

The affection differs from the cerebellar atrophy of "daft lambs" (WHITE and ROWLANDS 1945), because of the absence of blindness and deafness and especially the psychological disorders.

The nervous lesions in the cases of HUGHES and KERSHAW are only found in lambs which had the ataxia and not in those in whom one only noted changes in the fleece. No lamb in their series showed only neurological disorder. However TERLECKI and MARKSON have observed, after HUGHES and KERSHAW, already in 1958 analogous lesions and trembling lambs in other species and other regions in Great Britain.

Summary

1. We do not find lesions of muscles, nerves, anterior horns and spinal cord tracts. With other authors we stress the caution with which one should attribute any pathological significance to the alterations describes in new born animals. The study of strictly selected controls is from this point of view strongly indicated.

2. Neuronal lesions described in the brain stem and the cerebellum are sometimes found but are neither constant nor marked. One cannot retain them without reserve. In any case they do not constitute a diagnostic criterion.

3. The spongy transformation of the white matter, extending sometimes to the neighbouring cortex and exceptionally affecting the central grey matter, is the basis of diagnosis. It can be followed at all stages. Because of the existence, normally, of a gliosis of myelination in the same regions where the spongy transformation commences, it can be difficult to detect the very earlier stages of the affection. The first undoubted signs of an axial affection are venous stasis, the appearance of oedematous swelling of the glia and of the first spongy bullae or the first fissures in the ground substance.

4. By its structure, the pathological process suggests a disorder of metabolism of the nervous parenchyma, commencing in those areas where myelination commences. It shows itself with our present day histological technique in the form of a spongy imbibition followed by fissuring and cavitation by confluence of the cavities thus produced. This imbibition is associated with functional vascular disorders. The necrosis resolves as do the more familiar types of necrosis. There is little if any evidence of gliofibrillar organization. There are no signs of mesenchymal organisation. This may be due to the youth of the animals and the short period of their survival.

5. The structural characteristics of the disease process, on which is based in a certain number of cases the clinical picture of enzootic ataxia of lambs show that it cannot be compared with demyelinating disease nor the leucodystrophies described in man.

6. As far as we do today recognize its substrate, the congenital hypomyelogenesis and "B" disease are not the same as enzootic staxia of lambs.

We would like to thank here all the personnel of the Institute of Veterinary Medicine of the University of Thessalonica and the Institute of Pathology of Keldur of the University of Reykjavik for their valuable collaboration in taking our material under circumstances which were often difficult. We would like also to thank Dr. TERLECKI for having given us notes on the "Border disease" and the congenital Hypomyelogenesis and for having given us sections of material from this disease, and to Dr. A. L. WOOLF for having undertaken to translate this paper.

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Zusammenfassung

1. Es finden sich keine Läsionen in Muskeln, Nerven, in den Vorderhörnern und in den Rückenmarksbahnen. Mit anderen Autoren wird die Schwierigkeit betont, die pathologische Wertigkeit der bei neugeborenen Tieren gefundenen Veränderungen zu beurteilen. Deshalb ist es wichtig, genau ausgewählte Kontrollen mitzuuntersuchen.

2. Die im Hirnstamm und Kleinhirn beschriebenen neuronalen Läsionen sind weder konstant, noch ausgeprägt zu finden und daher nur mit Vorbehalt anzuerkennen. Keinesfalls stellen sie ein diagnostisches Kriterium dar.

3. Die spongiöse Umwandlung der weißen Substanz, die sich manchmal auf die benachbarte Rinde ausdehnt und ausnahmsweise auch die tiefen grauen Formationen betrifft, ist die Grundlage für die Diagnose. Sie kann in allen Stadien vorgefunden werden. Wegen des normalerweise gleichzeitigen Bestehens von Myelinisationsgliose in denselben Gebieten, wo auch die spongiöse Umwandlung stattfindet, kann die Aufdeckung der Frühstadien dieser Veränderung schwierig sein. Die ersten unzweifelhaften Zeichen einer Markschädigung sind: venöse Stase, Auftreten von ödematöser Schwellung der Glia, sowie der ersten Ödemlücken oder des ersten Defektes in der Grundsubstanz.

4. Der pathologische Prozeß legt durch seine Struktur eine Störung im Stoffwechsel des Nervensystems nahe, die in denselben Regionen beginnt, wo die Bemarkung stattfindet. Mit der heutigen histologischen Technik zeigt sie sich in Gestalt einer spongiösen Durchtränkung, gefolgt von Spaltenbildung und Höhenbildung durch Zusammenfließen der aufgetretenen Lücken. Diese Durchtränkung ist vergesellschaftet mit funktionellen Gefäßstörungen. Das nekrotische Gewebe wird wie bei den üblichen Nekroseformen verflüssigt. Es gibt kaum eine Faserglia-Organisation und keine Zeichen von mesenchymaler Organisation. Das dürfte dem jugendlichen Alter der Tiere und der kurzen Überlebenszeit entsprechen.

5. Die strukturellen Eigentümlichkeiten des Krankheitsprozesses, auf dem bei einer bestimmten Anzahl von Fällen das klinische Bild der enzootischen Ataxie der Lämmer beruht, zeigt, daß er weder mit den Entmarkungskrankheiten, noch mit den humanen Leukodystrophien verglichen werden kann.

6. Soweit wir heute das Substrat kennen, sind die angeborene Hypomyelogenese und die B-Krankheit mit der enzootischen Ataxie der Lämmer nicht identisch.

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