SWAYBACK :

A DEMYELINATING DISEASE OF LAMBS WITH AFFINITIES TO SCHILDER'S ENCEPHALITIS AND ITS PREVENTION BY COPPER

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WHETHER animals are insusceptible to many of the nervous disorders which afflict man is not yet fully known, but there are many nervous disorders which either do not occur in animals or have not yet been described. A few of the diseases which might come into this category include certain of the congenital and hereditary ataxias, while the gliomata and neuro-vascular disorders appear to be extremely rare. On the other hand, encephalitis due to a neurotropic virus occurs in nearly all the domesticated animals, a study of which has undoubtedly augmented knowledge of the pathogenesis of virus encephalitis as a whole. It would seem, therefore, that studies in comparative pathology have not yet been fully exploited in the study of diseases the ætiology of which in man remains obscure. In the case of the demyelinating maladies much work has been done, but so far all attempts to solve the ætiology have failed. Many interesting hypotheses have been suggested, none of which has had subsequent satisfactory confirmation. On these grounds the identification of any parallel condition in animals would be of value, as the animals could be studied at various phases of the disease and experiments could be tried out on a large scale denied to the medical worker.

The object of this paper is to bring to the attention of the medical neurologist work which has been done in connection with a condition in lambs which has some similarity to certain of the demyelinating disorders in man. As a result of this work a new approach may be suggested towards solving at least the mechanism of demyelination. The results of this work have already appeared in veterinary journals ; this paper is a summarized account of all the work which has been done up to the present and incorporated in these papers. (Innes, 1936a, 1936b ; Innes and Shearer, 1939 ; Dunlop, Innes, Shearer, and Wells, 1939). It is written more or less in the chronological order in which the work progressed.

"Swayback" is one of a number of names which have been given to this disease of young lambs—probably by the farmers on account of the main

symptom of incoordination. While attention has only been directed to the disease recently, there is plausible evidence that it has existed in England for generations.

The disease affects newly born or very young lambs from apparently healthy mothers ; either sex, single lambs, both of twins, or even all three of triplets may be affected with no proclivity for any of these. Rarely only one of twin lambs is affected, but in many such cases the other lamb develops the disease later. In most outbreaks the majority of cases are affected at birth, but some do not show symptoms (or are not observed) until they are a few weeks old. Whether the lamb is born affected or not until later, the symptoms are essentially the same. All cases show incoordination ; some are totally unable to stand and lie helpless ; others may rise with difficulty to collapse immediately ; some may be able to walk with a straddled gait ; while the very mild cases show only a slight weakness of the hind limbs.

Although this ataxia is always definite, there is no flaccidity and spasticity may be marked ; fits are not observed, tremors are inconstant, and the few reflexes which can be tested are not exaggerated. Many of the severely affected animals are blind. The disease is non-febrile and is usually progressive except for the mild cases. Under natural conditions the mortality rate is high, death occurring either from secondary infection, from exposure and/or malnutrition. The very mild cases may survive, and are often bred from later to give birth to healthy lambs. Ewes of any age and of any breed appear to be prone to give birth to affected progeny, although there is some indication that older ewes or those which have been on affected land for more than one year are more prone.

In Britain the disease has a wide geographical distribution and occurs in most of the counties of England and Wales, a few of the Border counties of Scotland, and as far north as Caithness. The incidence, however, has been one of the puzzling features of the disease, for it varies for no apparent reason on the same farm from year to year and in different farms in the same district in the same year. On some farms it has occurred annually, to then cease, or again to occur on farms on which it had been previously unknown. In some areas, e.g. in North Derbyshire, Yorkshire, and near the Mendips, it occurs almost as an annual " enzootic " disease at lambing time, and outbreaks have occasionally been so severe as to compel farmers to give up sheep-breeding. In the Derbyshire area during the lambing of 1938 there was a 10 per cent. mortality of over 3,000 lambs born, but the mortality may on some farms be 90 per cent.

A similar disease seems to have occurred in S. America (Argentina and Patagonia), Sweden, India, South Africa, and New Zealand. Although the pathology of the disease in these localities was never investigated, it is highly probable from the general accounts given that the workers concerned were dealing with the same entity. An identical disease also occurs in Australia, where, however, the pathology established in this country has been subsequently confirmed.

The pathognomonic lesions are confined to the nervous system. Gross

Fig. 1.—Brain, normal lamb : superior aspect ; for comparison with brains from Swayback cases ; the motor area in the superior frontal gyrus is shaded on the left side. About $\frac{1}{3}$ natural size.

Fig. 2.—Swayback: superior aspect of brain showing the collapsed appearance of the hemispheres after removal from the skull due to internal liquefaction and cavitation. Lamb ; 3 days old ; died. About $\frac{1}{3}$ natural size.

Fig. 3.—Swayback: horizontal sections of the cerebrum of two cases showing the gross destruction of white matter with extensive cavitation extending from the frontal to the occipital poles ; the grey matter remains as a thin shell around the cavities. Left photo: lamb ; 1 day old ; died. The twin of this animal was still-born and showed no gross lesions in the brain. Right photo: lamb ; 1 day old ; killed. The twin of this case showed similar changes. About $\frac{1}{3}$ natural size.

Fig. 4.—Swayback: coronal sections of the brain ; extensive symmetrical degeneration of cerebral white matter with cavitation, wasting of corpus callosum and relative preservation of grey matter. Lamb ; 5 days old ; died. About $\frac{1}{3}$ natural size.

Fig. 5.—Swayback: coronal sections of the brain ; diffuse symmetrical gelatinous degeneration of the cerebral white matter ; demarcation between grey and white matter blurred ; no cavitation ; the lesion here is reminiscent of that seen in Schilder's encephalitis. Lamb ; 6 days old ; killed. The twin of this case, also affected at birth, showed gross lesions similar to those seen in Fig. 6. About $\frac{1}{3}$ natural size.

Fig. 6.—Swayback: coronal sections of the brain ; appearances seen might be regarded as a stage between that in Figs. 4 and 5 ; diffuse bilateral degeneration, rather gelatinous in the frontal poles, with liquefaction and beginning cavitation in the occipital region. Lamb ; 2 days old ; killed. About $\frac{1}{3}$ natural size.

changes are present in the brain in most cases, and those described below have been seen in lambs of ages varying from birth to a few weeks old and occasionally in still-born animals. The bones of the cranium are thin, but the sutures united, and when the skull is opened there is evident an excess of cerebrospinal fluid. The cerebral convolutions are ballooned out, and if cut or lacerated collapse like a severe hydrocephalus. The cerebral lesions are symmetrical and consist of a gelatinous degeneration of the white matter, or liquefaction is so extensive as to cause cavitation which may extend from the olfactory to the occipital poles. The transition between degeneration and cavitation may often be seen at different levels of the cerebrum. The white matter is thus restricted to a wasted *centrum ovale*, corpus callosum, and capsules, while the cortex simply forms a thin shell of matter around the degenerated areas. In cases seen at an earlier stage cavitation may not be marked and the diffuse bilateral gelatinous degeneration is highly reminiscent of the lesions in Schilder's encephalitis. In this latter type the brain is soft and flabby, the convolutions rather blurred, and the demarcation between grey and white matter not clearly distinguished. The process has some predilection for the occipital poles and spreads anteriorly. Occasionally a secondary ventricular dilatation may be present, but macroscopic lesions are not found in the mid-brain, cerebellum, brain stem, cord, choroid plexus, and meninges. In a number of lambs showing only slight symptoms gross changes may not be found.

Histologically, demyelination is the constant and probably the primary lesion, the most severe type being represented by an almost total loss of cerebral myelin, affecting all zones in a diffuse manner. In a series of cases all gradations are seen, ranging from this severe type to small symmetrical foci of demyelination often present, for example, in those cases which showed no gross changes. Where liquefaction had been extensive the white matter was restricted only to a thin subcortical layer forming a margin to a cavity. The demyelination process seems to occur in a singularly rapid manner, as accumulations of stainable lipid, although frequently seen, are never present in gross amounts. Consequently it is not surprising that focal or perivascular collections of amœboid phagocytic glia are not a conspicuous feature of the lesion. Nissl or hæmatoxylin preparations show all gradations in these different cases, ranging from an apparently normal white matter to that of extreme *status spongiosus*. No gross patches of demyelination are found in the lower levels of the brain, but two well-defined nerve-fibre tracts in the cord are affected by a descending degeneration. These tracts are present (*a*) in the ventral column applied close to the median fissure and (*b*) forming another compact group in the dorso-lateral column close to the tip of the dorsal horn of grey matter. They correspond closely to the motor tracts which have been demonstrated in the sheep by experimental hemisection lesions, and probably represent combined pyramidal and rubro-spinal tract degeneration. The relative resistance of the nerve cells in all parts of the system form a conspicuous feature of the pathology. Pyknotic changes may occasionally be seen in the cells of the motor cortex and chromatolytic changes constantly in the cells of the red nucleus. Gliosis is easily demonstrable by suitable methods, although it is not so pronounced as

Fig. 7.—Normal lamb: coronal section of brain; Weigert-Pal. Compare with Swayback cases, Figs. 8 and 9. About natural size.

Fig. 8.—Swayback: diffuse bilateral demyelination to the extent of almost total loss of myelin with the exception of the optic chiasma. Lamb; 2 days old. About natural size.

Fig. 9.—Swayback: three-weeks-old lamb; diffuse bilateral demyelination of the hemispheres affecting particularly the subcortical zones; the fibres deep in the *centrum ovale* remain densely stained. About natural size.

Fig. 10.—Swayback: coronal section from frontal lobe near motor area, corpus callosum and ventricle below; diffuse demyelination most severe at the summits of the convolutions. Lamb; 11 days old; died. $\times 4$.

in comparable human maladies. It is necessary to emphasize : (a) that infiltrations by cells which are known to follow recognizable inflammatory agents in the nervous system are never found ; (b) that neuronophagia is never seen ; and (c) that a search for inclusion bodies failed.

The lesions thus offered a picture of a pathological entity which had hitherto not been described in domestic animals. Several conclusions were made at this time subsequent to the establishment of the pathology and there have been no fresh observations made to cause these to be altered. These are as follows:

1. The disease is one of a primary ante-natal origin.
2. The destruction of the cerebral myelin can only be regarded as an idiopathic disintegration of a substance which had been already formed *in utero*, the process is thus a true demyelination and not a myelin aplasia.
3. The state of myelination at the time the causative agent begins to operate must be an influential factor on the genesis of the disease. In this connection it must be obvious that the process does not begin until a relatively late stage of gestation, otherwise a greater degree of brain deformity than that seen would result.
4. While the history and pathology of many cases indicate that the disease is acute and progressive in nature, there is also a milder non-progressive type ; animals in the latter category survive to give birth to healthy progeny later.
5. In the mild type the causative agent must have then a minimal tempo of action or comes into action at a time late in gestation when only a small amount of myelin damage can take place. The cause is not operative beyond this period in foetal life as far as transference from the ewe is concerned, as it is a common practice to suckle healthy lambs on to ewes which have lost their lambs from "swayback" ; such foster lambs never develop the disease.
6. The tendency to early liquefaction of the cerebral lesions must be regarded as an exaggerated parallel to the difference in reaction between the brain of the child and adult to tissue destruction.
7. "Swayback" as a consequence has a number of features which are reasonably comparable to Schilder's encephalitis in the human, bearing in mind the possible differences in reaction which must almost necessarily occur in the lamb compared with a child. If Schilder's disease is only to be regarded as an anatomical entity the resemblance must be very close.

Ætiology

The failure which has attended attempts to solve the ætiology of the demyelination diseases of man rendered the prospect of success with this lamb condition a gloomy one. The disease showed so many puzzling features that it is not surprising now to note how the work took the simple course of the elimination of known causal disease factors. All attempts to isolate either a causal organism or virus either by cultural work or transmission experiments failed ; this negative result is of importance in view of the parallel negative ones which have been obtained repeatedly in connection with the demyelination diseases of man and monkey. Similarly, no evidence could be obtained to incriminate either breeding or hereditary factors, and it was soon apparent that deficiencies of any of the recognized vitamins or the more common minerals could also be eliminated as possible ætiological factors.

One other possible cause remained at that time as an obvious and necessary course of investigation ; this concerned the incrimination of lead in "swayback."

Lead-Poisoning and "Swayback"

The association of lead with certain of the demyelination disorders of man has often been suggested. It is not without interest, therefore, that a similar cause was assigned to "swayback" from several different sources.

In certain areas in England, e.g. in Derbyshire, it is an old belief of the farmers that "swayback" is a form of plumbism and a common name for the disease in this county is "belland." (The latter term originally meant in lead-mining areas the fine dust of lead ore ; as a consequence of the highly poisonous nature of the latter, the same term was applied to lead poisoning ; land which is known to contain large amounts of lead is thus often referred to as "bellanded.") Many of the fields in this area are irregularly traversed with what are known locally as "lead rakes"—remains of old lead mines—which have in course of time been overgrown with grass to which grazing animals have free access. The presence of lead in the soil and grass is said to give the latter a sweetish taste and animals eat it readily. Instances of "belland" in other animals (mainly horses and poultry) in which a paralysis of the hind limbs occurs are quoted by the farmer in support of his belief ; but the pathology of these cases has never been accurately determined. Independent observations in Australia also indicated that lead might be involved in the ætiology, as workers there found quantities of the metal in "affected" ewes' milk. As a result deleading experiments were made by the administration of ammonium chloride to pregnant ewes on affected land, with an apparent reduction of the disease in the progeny. In the absence of other proof at that time the position regarding lead as a cause was, however, very uncertain. From these observations it was obvious that lead could not be dismissed cursorily as of no moment, in

spite of the fact that "swayback" was not apparently confined to districts where lead outcrops are known.

Chemical analyses showed an extremely high lead content in the grass of many of the "affected" farms in the Derbyshire area and the livers of cases of swayback and their mothers contained lead in amounts which had to be considered highly abnormal. The difficulty, however, lay in the interpretation of the exact significance of these findings in the light of what was known about the disease. The ewes, for example, never at any time show signs of grave ill-health and certainly not of plumbism. Consequently it had to be considered that if lead was involved the ewes must ingest lead insidiously over a period of years and that for some reason the metal only affects the brain of the developing lamb. In view of Aub's work there are, of course, no great obstacles in the way of finding an explanation for this transient liberation of lead from the ewe's tissues during pregnancy and its transport through the placenta. It was, however, another matter to attempt to prove this experimentally.

From the pathological point of view there were no lesions present either in the ewes or the lambs diagnostic of plumbism. The lead line in the gums was only occasionally seen; an anæmia with punctate basophilia was not a constant feature; while X-ray examination of the bones showed nothing similar to the lead line in human lead poisoning. The cerebral lesions were of no diagnostic help, as there are no data available to indicate the appearances of lead encephalopathy in lambs.

The position at present is that until we know more about the exact ætiology of "swayback," lead cannot be ignored as a possible complicating causative factor. "Swayback" need not be, and in fact cannot be, a direct form of plumbism. But we do not know how the presence of lead in the diet might affect the assimilation of other substances, or when present in the body tissues how it might affect normal myelin metabolism. The urgent need at the moment would seem to be the establishment of more exact criteria which would enable the recognition of the early ætiological connection between lead and injuries to the animal organism.

Copper Deficiency and "Swayback"

The idea that a "trace element," such as copper, might be associated with the disease no doubt took origin from observations in a field divergent from that of nervous disorders, namely, the discovery of cobalt as a factor in controlling certain nutritional anæmias in sheep in Australia. This suggestion of a copper deficiency arose from work by Bennetts (1937) in W. Australia. Twelve pregnant ewes on "affected" land were given periodic doses of copper sulphate during pregnancy; their lambs failed to develop "swayback," while in the control group receiving no copper the incidence was 100 per cent. The conclusions of this work were as follows:—pregnant ewes pastured on "affected" land developed a macrocytic hyperchromic anæmia, and as a result their lambs were affected with "swayback." The copper content of the blood, liver, and

milk of these anæmic ewes was much below normal. The feeding of copper caused a marked response in the blood picture, the anæmia was thus cured and the progeny were not affected with "swayback." This anæmia was considered to be analogous to pernicious anæmia, although it did not respond to liver therapy. A few analyses of the grass showed that there was no copper deficiency present and the pathogenesis awaited further explanation.

Copper has for long been known to play some part in normal erythropoësis, although its exact rôle is still unknown. This was, however, the first time that any suggestion had been made regarding a vital connection between a "trace element" and myelin.

In 1938 investigations were begun along these lines which ultimately involved much hæmatological and chemical work and finally a large-scale field experiment to determine more accurately the prophylactic value of copper in "swayback."

Hæmatological examinations of many ewes in "swayback" areas compared with suitable control animals showed that while an anæmia was occasionally present in ewes which gave birth to "swayback" lambs, it was not constantly related to the disease of the progeny. An anæmia was found in ewes which also gave birth to healthy lambs in and away from affected "swayback" areas. Also no evidence was obtained to show that this anæmia was macrocytic and hyperchromic in type; macrocytosis, evident from a series of Price-Jones' curves, was undoubtedly absent and there was no evidence to show that the anæmia was even hyperchromic. It was concluded that the observations of Barcroft regarding the occurrence of a raised blood volume and decreased hæmatocrit reading in normal pregnant ewes might indeed indicate that this "anæmia", which we found, could be partly explained on this physiological basis. There was similarly no uniform change in the blood picture of "swayback" lambs.

Chemical analyses showed that the copper content of both the blood and liver from "swayback" cases was much lower than that of normal lambs of the same age and that the copper content of the ewe's blood was likewise low. Although not constant there also seemed to be a relationship between the blood Cu of the affected lamb and its mother. At the same time there was the puzzling feature that the Cu content of the blood of ewes (as a whole) in the Derbyshire area was much lower than that in ewes from a control area and in some cases was of the same low magnitude as in ewes which gave birth to "swayback" lambs. Grass analyses showed that there was no Cu deficiency present.

A field experiment was carried out in the centre of a "swayback" area on Bradwell Moor, Derbyshire. Ewes were obtained on loan from farmers in this district to act as our experimental flock, while the experimental area consisted of 300 acres which had been divided off into four separate but contiguous enclosures; another field about a mile away acted as an additional control area. All the ewes were numbered for identification purposes and divided into control and experimental groups. One control group was kept in this main experimental area, while the other control group was kept in the isolated enclosure. The experimental groups comprised two main flocks of animals

which received during pregnancy pure salt licks containing 0.3 per cent. and 1 per cent. Cu (as CuSO_4) respectively ; animals from these two flocks were drafted on to this lick treatment at various times during pregnancy, from 23rd of December, 1938, 11th January, 1st March, 23rd March, 1939. (The gestation period in the sheep is about 21 weeks, lambing beginning in this area about the middle end of March, so that this meant the ewes would be receiving treatment for roughly 12, 10, 7, and 4 weeks before parturition.) The animals were moved around the four enclosures in the area every three weeks, so that all ewes received virtually the same treatment. The results of this feeding experiment are shown in tabular form below.

NUMBER OF LAMBING EWES, BIRTHS, DEATHS, AND CASES
OF "SWAYBACK" IN THE VARIOUS GROUPS.

GROUP.	NUMBER OF EWES.*	NUMBER OF LAMBS BORN.	NUMBER OF LAMBS DIED.	CASES OF "SWAYBACK."†	DEATHS FROM ALL OTHER CAUSES.‡	NUMBER OF EWES WITH "SWAYBACK" LAMBS.
Control A ..	40	63	40	24 (1)	18	16
Control B ..	40	60	28	12 (2)	17	10
Total	80	123	68	36	35	26
Experimental C. 1 per cent. Cu from						
23rd Dec. ..	15	27	7	0	7	0
11th Jan. ..	10	16	4	0	4	0
1st Feb. ..	11	17	5	1	4	1
23rd Feb. ..	10	17	4	1	3	1
Total	46	77	20	2	18	2
D. 0.3 per cent. Cu from						
23rd Dec. ..	32	50	20	0	20	0
11th Jan. ..	15	20	3	1	2	1
1st Feb. ..	16	25	7	4	3	3
23rd Feb. ..	18	28	13	8 (3)	6	6
Total	81	123	43	13	31	10

* The numbers in this column are less than the original number placed in these groups at the beginning of the experiment owing to deaths, barren ewes, and animals which were missing at the final identification. There was no evidence whatsoever that the mortality in the ewes was due to the copper treatment ; the causes of death included obvious infection, pneumonia, one case of cirrhosis, and deaths during parturition from obstetrical troubles.

† The cases of "swayback" include a few animals which showed symptoms shortly after birth and which were not killed. (1) two cases ; (2) one case ; (3) one case.

‡ This includes still-born lambs.

It will be seen that the incidence of "swayback" is highest in the control group (A) which had been kept away from the main experimental area and slightly lower in the other control group. Compared with this incidence, the absence of cases of the disease in the experimental groups which received either 0.3 per cent. or 1 per cent. Cu lick from 23rd December, 1938, until lambing is striking and convincing proof of the efficacy of copper in the prevention of the disease. The incidence increased accordingly as copper treatment was delayed, so that in the group which received Cu licks for only a short time before lambing (from 23rd March, 1939) there is little difference in the number of "swayback" lambs to that of one of the control groups (B).

These results are of significance, although we cannot offer at this stage any explanation of the mode of action of copper and from this of the pathogenesis of the disease. The disease is not one of a Cu deficiency *per se* in the ewe, as analyses of the herbage showed no difference in the Cu content compared with control pastures. It might therefore be simply a hazard to speculate at this stage, but there are some explanations which may be tentatively offered: (a) A depletion of Cu reserves in the ewe takes place before the birth of an affected lamb; this is reflected in a reduction of the Cu stores of the newly born "swayback" lamb compared with a normal one. (b) The level of Cu in the blood of the ewe is not the primary factor which determines the development of "swayback" in the lamb, as low levels are sometimes found in ewes on the same farm which give birth to healthy progeny. (c) The Cu deficiency might therefore be a relative one which could be explained either by the element being present in an unsuitable form in the grass or by the presence of some other factor in grass which would inhibit the absorption of Cu or by the presence of alimentary dysfunction in the ewe inhibiting the Cu gut absorption and/or an increased rate of excretion of Cu in the ewe.

The aetiology of this demyelinating disorder in lambs can thus be regarded in a new light, although much work will still be necessary to determine the exact physiological rôle of copper in relation to myelin metabolism. No suggestion is made that other demyelination diseases have a similar causal foundation, as it is highly probable that the problems associated with them are several and not one and that the demyelination lesion is only the limited reaction of the nervous system to a number of factors. The work does, however, suggest a method for a more intimate study of the mechanism underlying the process of demyelination.

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