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MALDRONKSIEKTE IN CATTLE: A NEURONOPATHY CAUSED BY *SOLANUM KWEBENSE* N.E. Br.*

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ABSTRACT

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A neurological disease of cattle (maldronksiekte), occurring in a localized area of the Northern Transvaal, was experimentally reproduced by feeding *Solanum kwebense* plants to cattle. The disease is characterized by temporary loss of balance and transient epileptiform seizures precipitated by a variety of stimuli, such as exercise, handling (dipping, loading, etc.) and fright. When not disturbed, most affected animals appear to be completely normal. The most conspicuous histopathological lesion is a neuronopathy manifested by vacuolar degeneration and eventual necrosis of neurones, particularly of the Purkinje cells in the cerebellum. An atrophy of the cerebellar cortex is seen grossly.

The history, clinical signs and experimental reproduction of the disease, as well as the pathology of 4 experimental and 18 natural cases, are described.

Résumé

L'ÉPILEPSIE CHEZ LE BOVIN: UNE NEUROPATHIE DUE À LA PLANTE SOLANUM KWEBENSE. *N.E.Br.*

En leur faisant manger la plante Solanum kwebense, *les auteurs ont pu réproduire chez des bovins une affection nerveuse (l'épilepsie bovine), maladie propre à une région localisée du Transvaal du Nord. Les manifestations caractéristiques de la maladie sont une perte d'équilibre et des attaques épileptiformes suscités par diverses excitations comme l'exercise, la manipulation (le plongement, le chargement etc.) et l'effroi. A l'abri de toute excitation, la plupart des animaux affectés parait avoir une santé en apparence la plus parfaite. La lésion microscopique la plus marquée est une neuropathie comprenante la dégénérescence vacuolaire des neurones aboutissante à la nécrose de ceux-ci surtout au niveau des cellules Purkinje du cervelet. Une atrophie de l'écorse cérébelleuse est visible a l'autopsie. Les auteurs présente l'anamnèse, les symptômes et la reproduction expérimentale de la maladie, ainsi que les lésions anatomo-pathologiques d'après* 4 *cas expérimentaux et* 18 *cas devenus malades dans la nature.*

INTRODUCTION

Maldronksiekte (literally translated as mad- or crazy-drunk-disease) is an Afrikaans name coined by South African farmers for a disease in cattle characterized by epileptiform seizures. Vallendesiekte (epilepsy) is another Afrikaans name which is sometimes used. In this article the history, clinical signs, pathology and aetiology of the disease are described.

HISTORICAL REVIEW

Occurrence

The first reports of a peculiar disease of cattle were received in July 1953 from the Rooibokkraal area in the Rustenburg district of the Transvaal. Few details were recorded, but it appeared that the disease was characterized by a temporary loss of balance which was precipitated by excitement. Affected animals were said to often fall down or to injure themselves by walking into trees and fences. After a few unsuccessful attempts to rise, such animals would regain their feet and stagger about drunkenly for a short while before making what appeared to be a complete recovery, and walking off as if nothing had happened. The first recorded cases occurred on the farm Krokodilstaart. During March 1955 the State Veterinarian, Rustenburg, reported that the disease was on the increase on the original farm and that cases were occurring on various other farms in the vicinity. K. Schulz & T. F. Adelaar (unpublished report, 1955) conducted an investigation during the winter of that year but were unable to elucidate the nature of the disease.

A detailed investigation conducted by W. L. Jenkins (unpublished report, 1964) into the distribution and incidence of the disease revealed that it had also occurred on the farms Rooibokkraal, Buffelsdraai, Van Stadenshoek, Olifantsdrift, Klipvley and Lyon. While most cases were seen between February and March the incidence of the disease was variable, nor did it occur with regular intensity each year, but appeared to be more common during particularly dry years.

Area affected

The disease occurs in the North-western Transvaal in the vicinity of the confluence of the Crocodile and Marico rivers (Fig. 1). The vegetation in this area is classified as geelhaak veld, which is a variation of the arid, sweet bushveld (Acocks, 1975) and is covered by tree savanna of varying density. Various *Acacia* species predominate, *A. erubescens* (geelhaak), *A. giraffae* and *A. senegal* being the most common, and *Grewia flava* (rosyntjiebos), *G. monticola* (kruisbessie) and *Rhigosum brevispinosum* (driedoring) are the most important shrubs. The grasses consist mainly of perennial species e.g. *Panicum maximum, Digitaria pentzii, Aristida congesta* and *Eragrostis rigidior.*

Animals affected

Cattle only have been observed to contract the disease under natural conditions. Although some farmers claim that horses, donkeys and goats are also susceptible, no confirmed cases have been encountered in these animals and the disease could not be produced experimentally (*vide infra*) in them. There is no breed, age or sex predisposition to the disease and cases have been observed in cattle at any age from 6 months up to 10 years.

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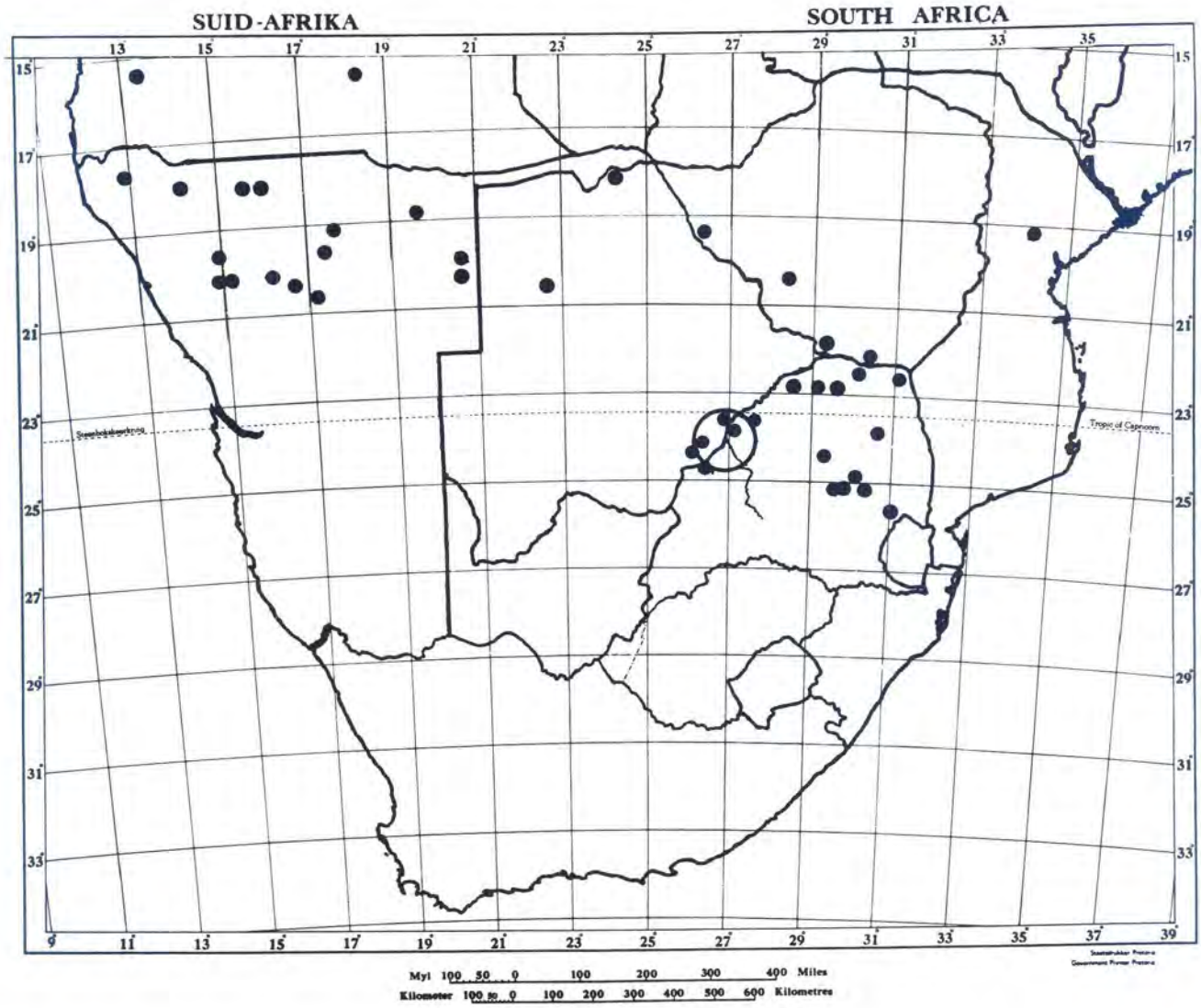


FIG. 1 The distribution of *Solanum kwebense*. The circle indicates the area in which the disease occurs

Morbidity and mortality

Morbidity varies from 1–70%, whereas mortality rates as high as 30% have been reported. It should be pointed out that very few animals die from the disease *per se*, but that many affected animals succumb by misadventure, such as by drowning during dipping or having to be destroyed on account of severe injuries sustained during falling episodes.

Clinical signs

The clinical signs of maldronksiekte are related to malfunction of the central nervous system (CNS). Although some disturbance of respiration (viz. arrhythmia and mild expiratory dyspnoea) may be seen during an attack, these signs are probably the result of abnormal positions assumed when animals fall down.

It is usually necessary to disturb, frighten or chase affected animals to elicit symptoms of the disease. The clinical signs during a typical attack may be summarized as follows: Affected animals appear to graze normally, with normal posture and gait until disturbed, when signs, varying from gross epileptiform seizures with collapse to only a mild lateral head tilt with slight ataxia and muscle tremors may be seen. Mild cases may show only a tilted head of rigid neck, often accompanied by slight degrees or hypermetria and dysmetria. Other animals adopt an attitude of 'star-gazing', with the head raised and swaying from side to side, and a rigidly outstretched neck. They stumble sidelong in a crouching posture with stiff legs and a wide-based stance, often stumbling or crashing into obstructions.

Severely affected animals fall down, often landing with their full mass on their muzzles, knees or briskets. After falling, they struggle to regain their feet, frequently with the head folded in under the body, or in a position of opisthotonos. A peculiar staring expression is seen in the eyes at the commencement or during an attack. The eyes are also rotated upwards, showing the white of the sclera with lateral nystagmus, both before the animal falls and while it is down. Continual urination and defaecation may be seen during or following an attack. After regaining their feet, animals show generalized muscle tremors, most conspicuously over the flank and shoulder areas.

A remarkable feature of the disease is the rapid recovery following an attack. Fallen animals quickly re-orientate themselves, regain their feet and appear normal within a few minutes.

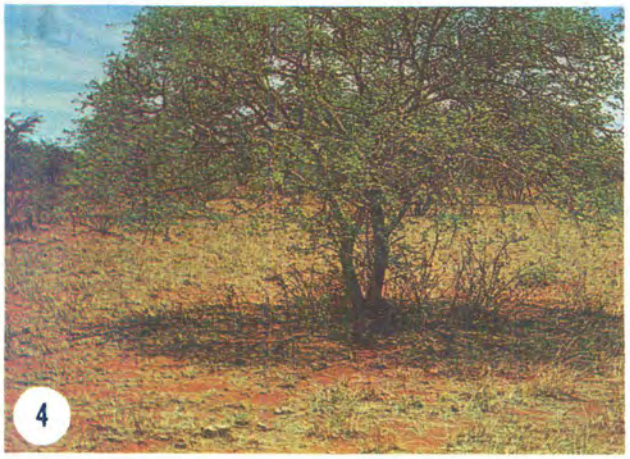


FIG. 2 A dense stand of *S. kwebense* underneath a geelhaak (*A. erubescens*) tree, with *E. rigidior* growing in the open

FIG. 3 A young *S. kwebense* plant. Note the absence of grass in its immediate vicinity

FIG. 4 Almost bare stalks of *S. kwebense* left by grazing cattle in a severely overgrazed area

FIG. 5 Flower and ripe fruit of *S. kwebense*

As a result of frequent falling, secondary trauma e.g. broken horns, fractured teeth and jaws, bruising of the mouth, brisket and legs are commonly present. Although there is an obvious loss of balance during an attack, there is apparently no impairment of vision or loss of consciousness. If left undisturbed, affected animals never really look normal. They appear nervous and are the first to move away should a herd be approached in the veld. In badly affected animals, loss of condition is a notable feature.

Recoveries were reported by some farmers, but they were apparently the exception. In affected free-ranging cattle, symptoms can be induced readily by frightening, chasing or handling them and, in pronounced cases, by merely tapping a horn. It becomes increasingly difficult to produce symptoms in affected animals when they are stabled and handled regularly since they adapt to their surroundings. K. Schulz & T. F. Adelaar (unpublished report, 1955) reported that after 2 months of stabling and regular handling, a young steer, which showed marked symptoms under natural conditions, failed to react to the usual stumuli. Typical symptoms of the disease could, however, still be induced if the animal's head was forcibly lifted and suddenly released.

Aetiology

Results obtained by investigators since 1955 (K. Schulz & T. F. Adelaar, unpublished report, 1955; W. L. Jenkins, unpublished report, 1964) indicated that infectious agents, mineral deficiencies or congenital and hereditary factors were probably not involved in the aetiology of the disease but that maldronksiekte might be caused by the ingestion of a plant.

K. Schulz & T. F. Adelaar (unpublished report, 1955) noticed the prevalence of *Solanum* and *Kalanchoë* species on the affected farms. They disregarded the *Solanum* species on the grounds that the symptoms did not resemble those caused by solanine and that various species of this plant are widely distributed throughout southern Africa in areas where the disease is unknown. No mention is made by them, however, of the particular species of *Solanum* noticed. W. L. Jenkins (unpublished report, 1964) dosed cattle with *Kalanchoë paniculata* and *K. rotundifolia*, obtained from the Rooibokkraal area, with negative results.

During February 1972, a local investigation was again carried out in the Rooibokkraal area (J. G. Pienaar, T. S. Kellerman, J. Vahrmeijer & J. M. Olivier, unpublished report, 1972). It was found that some camps on farms with a history of a high incidence of the disease showed signs of severe overgrazing. Camps adjoining the 2 rivers, although also overgrazed, were free of the disease. These river camps differed from the other camps in that the soil was clayey to loamy with *A. tortilis* (haak-en-steek) as the predominant tree, and no *A. erubescens*. Problem camps were in all instances located on higher sandy soil, or so-called geelhaak veld, where *A. erubescens* was the most common tree. On the badly overgrazed areas in the geelhaak veld, the palatable perennial grasses, growing in the open, were completely replaced by the unpalatable *E. rigidior* (Fig. 2). Similarly, *P. maximum*, which only grows in the shade under trees and which is a highly palatable and nutritious grass, was replaced by thick stands of *S. kwebense* (Fig. 2 & 3). A definite correlation existed between the occurrence of the disease and the camps with severely disturbed vegetation where *E. rigidior* and *S. kwebense* formed the main grazing plants. *S. kwebense* was readily grazed by cattle in these camps (Fig. 4). It was thus decided to investigate the toxicity of this plant and, as will be shown, *S. kwebense* was found to be responsible for the disease.

Description and Distribution of the Plant

Family:	Solanaceae
Name:	*Solanum kwebense* N.E. Br. (Thiselton-Dyer, 1906; Merxmüller, 1969).
Synonyms:	*S. hierderitzii* Schinz *S. upingtoniae* Schinz *S. tenuiramosum* Dammer *S. chondropetalum* Dammer
Common names:	Rooibessie, bitterappel
Description:	An erect, somewhat laxly branching shrub up to 2 m high

Branches rather slender, woody at the base. At first densely covered with a close, white or pale yellow stellate tomentum. Then pruinose, bark finally dark and glabrous, unarmed or with a few small spines. *Leaves* alternate, lanceolate to ovate-lanceolate, obtuse, broadly cuneate or acute at the base, entire, 25–90 mm long and 10–40 mm broad, grey-green, covered with minute stellate adpressed hairs above, more densely so beneath, nearly glabrous on both surfaces when mature. *Cymes* small, 2–10 (sometimes 1) flowered, stellately tomentose, peduncles 3–8 mm long, pedicels 4–12 mm long. *Flowers* usually tetramerous, rarely pentamerous, 10–17 mm across. *Calyx* campanulate, 3 mm long, stallately tomentose outside, 4-lobed nearly half-way down, lobes deltoid-ovate, subacute. *Corolla* rotate or reflexed, 4-lobed, white, mauve, blue or purple, glabrous inside, lobes 3 times as long as the tube, 8–10 mm long, 3 mm wide, oblong-lanceolate, subacute. *Stamens* 4, uniform, filaments very short, anthers yellow, 5 mm long, linear-oblong, pores terminal. *Berries* globose, 5–10 mm in diameter, green at first, becoming yellow, then orange-red and finally scarlet when ripe (Fig. 5). The flowers and fruits are borne more or less simultaneously from about October to May. *S. kwebense* can be distinguished from other *Solanum* spp. in the same areas by its pedunculate cymes and spineless, entire, discolorous leaves.

Distribution: The distribution of *S. kwebense* is illustrated in Fig. 1. It has been recorded in the following areas:

South West Africa: Kaokoveld, Ovamboland, Okavango, Etosha, Grootfontein, Outjo, Otjiwarongo

Botswana: Ngamiland, Chobe, Kgatleng

Transvaal: Soutpansberg, Potgietersrus, Pietersburg, Letaba, Rustenburg, Waterberg, Lydenburg, Nelspruit

Habitat and ecology: S. kwebense can be found on flats, dunes or hill slopes and on sandy, loamy or stony soil such as calcified dolomite or weathered granite. It is common among grass in dry thorn scrub and mixed bushveld, in association with *Acacia, Lonchocarpus, Boscia, Catophractes, Colophospermum mopane* and *Spirostachys africana*. *S. kwebense* often grows in the shade of trees, especially in overgrazed veld. This shrub has been collected at altitudes from 370–1 500 m.

MATERIALS AND METHODS

Dosing trials conducted at Onderstepoort Veterinary Research Institute

The animals used for these trials were crossbred Afrikaner calves, approximately 6–12 months old.

Twigs of *S. kwebense* plants were collected from camps where cases had occurred during the latter half of summer (December–March), dried in the shade, milled, and dosed to animals (Table 1). The material was administered, either by stomach tube or mixed in a ration daily, except during week-ends and on public holidays. Besides *Solanum* plants, each animal received a standard ration consisting of grain concentrates, green lucerne, and teff hay.

The animals were clinically examined daily and the following routine chemical-pathological determinations were regularly done on the blood: sedimentation rate, haemoglobin percentage, serum glutamic oxaloacetic transaminase, total bilirubin, serum urea nitrogen, blood glucose, total plasma protein, and serum calcium, sodium and potassium.

Clinical signs were induced by forcibly raising the head of the animal (Fig. 6) for about 60 seconds and then suddenly releasing it. This method was adopted as a result of the observation by K. Schulz & T. F. Adelaar (unpublished report, 1955) that severe clinical signs could be induced by raising the heads (HR test) of affected animals which had adapted to regular daily handling.

Those that reacted positively were euthanized with pentobarbitone sodium or immobilized with suxamethonium chloride (0,2 mg/kg i/v) immediately before their throats were cut for post mortem examination. Specimens were collected from various organs, fixed in 10% buffered formalin and processed according to standard procedures. Sections were stained with haematoxylin and eosin (HE). Brain sections were also stained by the following histochemical methods, according to Pearse (1961): periodic acid Schiff (PAS), for carbohydrates; peracetic acid Schiff (PAAS), for unsaturated lipids; oil red O and Sudan black, for neutral lipids; and Nile blue sulphate and copper pthalocyanin, for phospholipids.

Investigation of field material

Four naturally affected cattle were brought to the Research Institute for clinical, chemical-pathological and pathological studies. In addition, specimens of the CNS and other organs of 14 naturally affected animals were examined.

RESULTS

Dosing trials with cattle

Clinical signs

Calf 1

Calf 1 was given 43,4 kg of dry *S. kwebense* plants divided into 43 doses of 5,0–7,5 g/kg each over a period of 59 days (Table 1).

From Day 29 onwards, the calf sometimes appeared to be slightly restless and nervous, often pushing lightly with its muzzle against objects. These pushing episodes, lasting from a few seconds up to a few minutes, recurred intermittently with decreasing frequency up to Day 84. None of the other 3 calves showed clinical signs of this nature.

The first definite response to the HR test appeared on Day 65 when the calf momentarily lost its balance and developed a slight muscular tremor in the shoulders. Three days later it began to fall down with typical epileptiform seizures when the HR test was applied, this sometimes happening even before the head was released (Fig. 7). Once on the ground it

TABLE 1 Dosing trials with *S. kwebense*

Experimental animal	Approximate age (years)	Initial live mass (kg)	Dosing regimen (g/kg/day) × n*	Total mass dosed (kg)	Number of doses given	Period dosed (days)	First epilepti-form seizure (day)	Duration of experiment (days)
Calf 1	½	127	5,0 × 5 7,5 × 38	43,4	43	59	68	121
Calf 2**	½	132	5,0 × 9 7,5 × 73	96,6	82	116	84	
		228	5,0 × 5 7,5 × 39	71,9	44	66	26	448
Calf 3	1	230	5,0 × 5 7,5 × 35	64,6	40	58	53	556
Calf 4	1	207	5,0 × 5 7,5 × 35	59,1	40	58	84	556
Donkey***	2	200	2,5 × 16 3,75 × 14 5,0 × 7	25,5	37	39	—	109
Goat 1	4	43	5,0 × 9 7,5 × 26	10,0	35	49	—	136
Goat 2	3	38	5,0 × 9 7,5 × 29	9,6	38	52	—	136
Sheep 1	3½	28	5 × 1 10 × 1 20 × 1 25 × 1	1,7	4	21	—	30

*n = number of doses
** This animal was dosed in 2 successive years
*** This animal ate the material mixed in ration

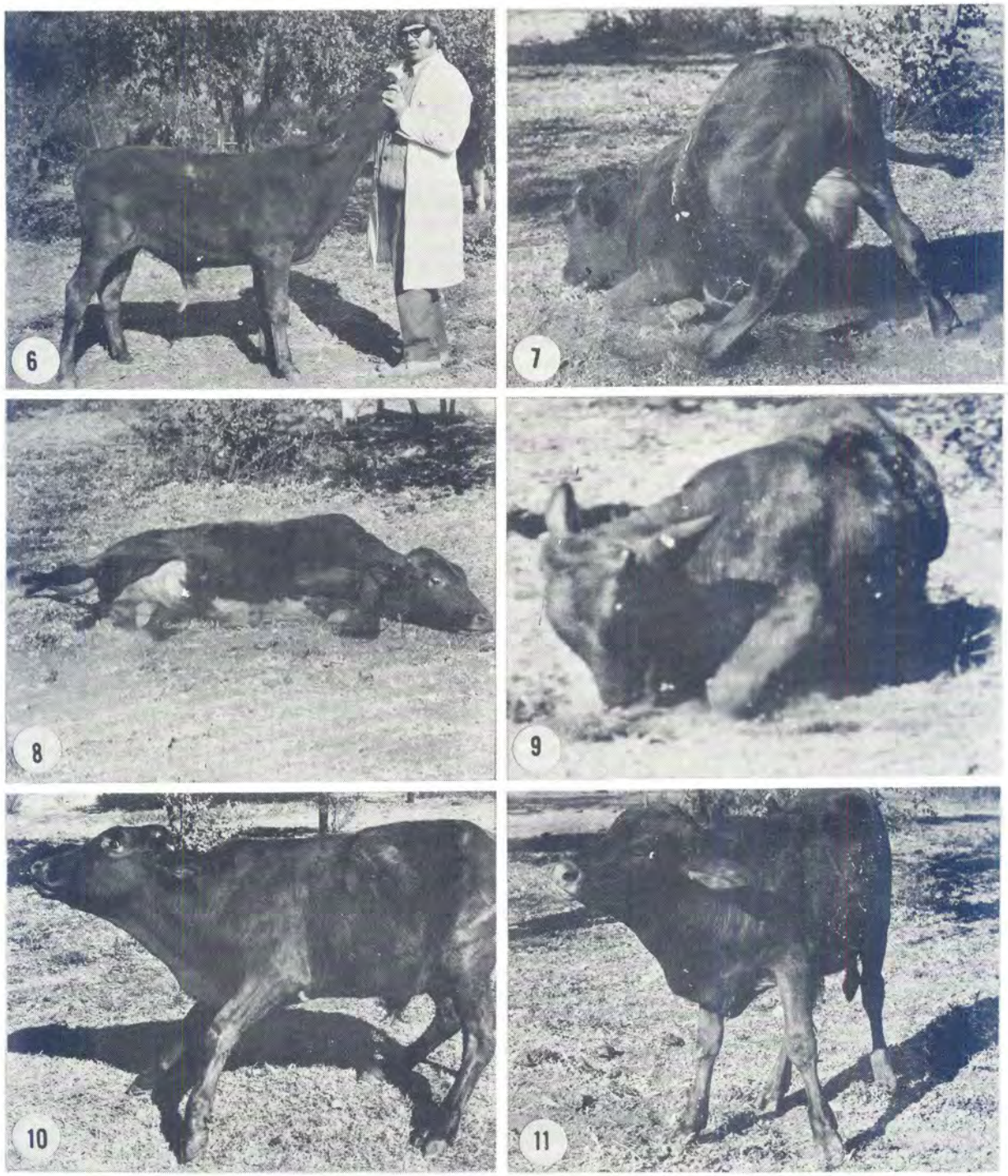


FIG. 6 The head raising (HR) test being applied

FIG. 7 After the release of the head, the animal falls down on its muzzle and knees

FIG. 8 & 9 The animal rolls over to a lateral recumbency and then, after struggling to a position of sternal recumbency it staggers to its feet.

FIG. 10 After regaining its feet, the calf stumbles sideways in a crouching posture with a wide-based stance. Note the rigidly stretched neck, the raised head and blank staring expression in the eyes

FIG. 11 Calf showing a lateral head tilt, wide-based stance and staring eyes

would struggle for a minute or more to orientate itself to a sternal position (Fig. 8 & 9) before staggering to its feet, and then stumble drunkenly for a few yards. The severity of symptoms diminished, if the HR test was repeatedly applied over a short period.

The onset of symptoms was even more rapid if both eyes of the animal were closed when the test was applied. Although this procedure did not always lead to the animal's falling down, nystagmus was a constant symptom. Sometimes the calf only stumbled sideways in a crouching posture, with a wide-based stance, its neck stiff and outstretched, the head raised in a star-gazing position (Fig. 10) and tilted to one side with a blank staring expression (Fig. 11) and obvious nystagmus. Within 30–60 seconds after such an attack the animal assumed a completely normal posture and gait. The signs described above were also seen after the animal had regained its feet following a fall.

Calf 1 was autopsied on Day 121.

Calf 2

Calf 2 received 96,6 kg of *S. kwebense* in 82 doses of 5,0–7,5 g/kg in 116 days.

The first clinical signs, namely slight temporary disorientation and mild tremors of the head and neck muscles, appeared on Day 24. Thereafter the response to the HR test gradually increased until the animal fell down with typical epileptiform seizures (Day 84–Day 120). After dosing had ceased (Day 116), the clinical signs gradually diminished. The steer fell down only once more (Day 120) and then progressively recovered to the stage where only nystagmus could be induced (Day 141).

Dosing was interrupted after Day 116 for 170 days owing to lack of plant material. When fresh material became available in the summer of 1973/74, 71,9 kg of the dry plant was administered to the steer in 44 doses of 5,0–7,5 g/kg over 66 days. Nystagmus and mild, transient disorientation were noticed after the head was lifted on Day 9. Lifting the head on Day 26 and Day 33 caused the steer to fall down, but after that the response progressively diminished. By Day 69 a slight head tilt, nystagmus and mild disorientation only could be elicited, and even this response eventually diminished to the point where it was almost negligible. The steer was destroyed for autopsy on Day 162.

Calf 3

A total of 64,6 kg *S. kwebense* material was administered to this steer in 40 doses of 5,0–7,5 g/kg over a period of 58 days.

The first reaction occurred on Day 39 when the muscles of the shoulders trembled after application of the HR test. Lifting the head on Day 49 produced disorientation, a staggering gait, nystagmus and slight tremor of the muscles. On Day 53 the animal staggered backwards, sank down on its haunches and somersaulted onto its back. A few seconds later it stood up again, showing typical clinical signs. Between Day 53 and Day 85 it usually fell down with epileptiform seizures when the head was lifted. This animal was also remarkable in that it was the only one to develop epileptiform seizures spontaneously. It fell down with seizures while grazing on Day 72 and on Day 85 it suffered another attack while being mass-measured. After Day 91, however, the clinical signs rapidly diminished. The animal no longer fell down and by Day 108 there was scarcely any response to the HR test. The steer was then kept under observation until it was destroyed for post mortem examination on Day 556.

Calf 4

In a similar experiment, 59,1 kg of the material was given to this steer in 40 doses of 5,0–7,5 g/kg over 58 days. The response was never as marked in this case as in that of Calf 3. Application of the HR test at first caused mild signs, such as disorientation, etc. (Day 25), which grew in intensity until the animal sometimes fell down (Day 84–Day 98). Thereafter the response diminished in magnitude until Day 115 when lifting the head had little effect. As in the previous case, Calf 4 was rested until Day 556 before it was destroyed.

Dosing trials with other animals

The donkey, 2 goats and 1 sheep did not show any clinical signs suggestive of CNS involvement at any stage and were discharged from the experiment. The amounts of plant material dosed to these animals are summarized in Table 1.

Chemical-pathological findings

No conspicuous chemical-pathological changes could be found in the blood of either naturally or experimentally intoxicated animals.

Pathological findings

Since lesions in the CNS, identical to those in the natural cases, were found in the 4 experimental animals, for the purpose of this article, no distinction will be made in describing the lesions of the 2 groups.

Gross pathology

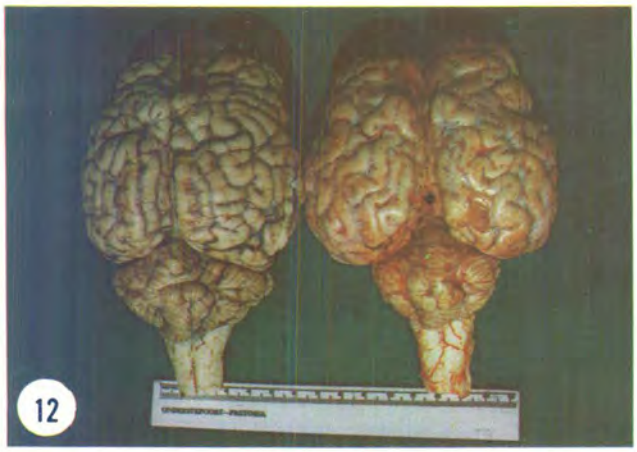
Except for the secondary traumatic lesions sustained during falling described above, the only other gross lesion present was a varying degree of atrophy of the cerebellum (Fig. 12 & 13). In pronounced natural cases the reduced size of the cerebellum was easily recognized. In milder natural cases and in the experimental cases, it was usually necessary to compare the size of the cerebellum with that of a normal animal before any difference could be discerned.

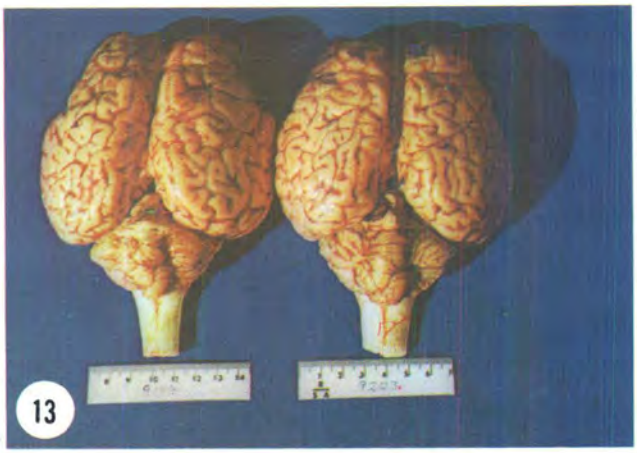
The atrophy occurred uniformly throughout all the lobes of the cerebellum. Examination of gross coronal sections of the cerebellum revealed that numerous folia were markedly smaller, giving the cortex a thinned-out appearance (Fig. 14).

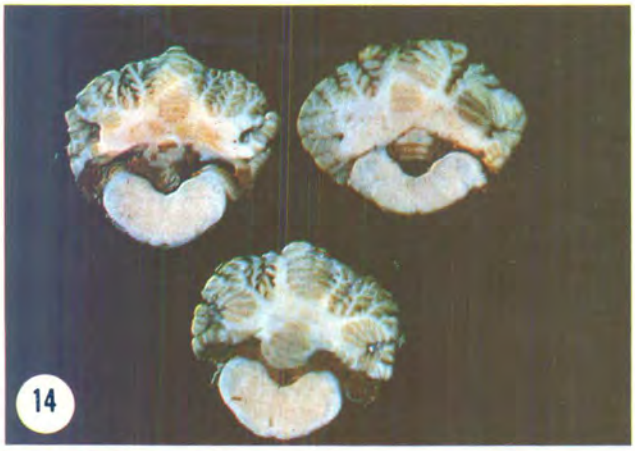
Histopathology

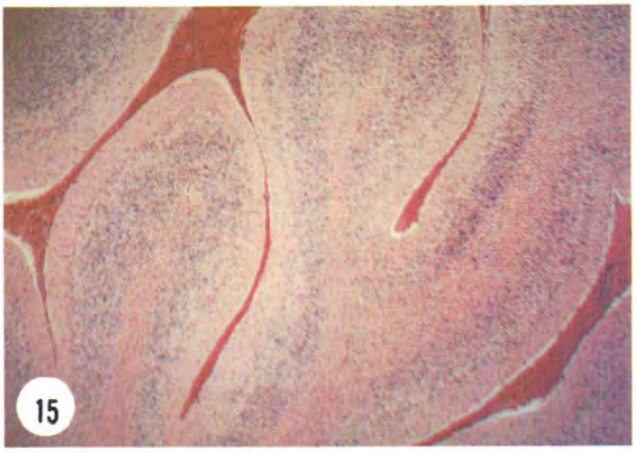
Lesions were found only in the CNS where the most striking feature was the paucity or, in many instances, the complete absence of Purkinje cells in some of the folia of the cerebellar cortex (Fig. 15 & 16). This was not localized in any particular lobe of the cerebellum, but folia throughout the cortex were affected to a greater or lesser degree. The remaining Purkinje cells showed a variety of changes. The cytoplasm of the majority was swollen and contained numerous small vacuoles. In many cells the vacuoles were located towards one pole of the cell, which was then ballooned (Fig. 17), while in others they completely filled the cytoplasm.

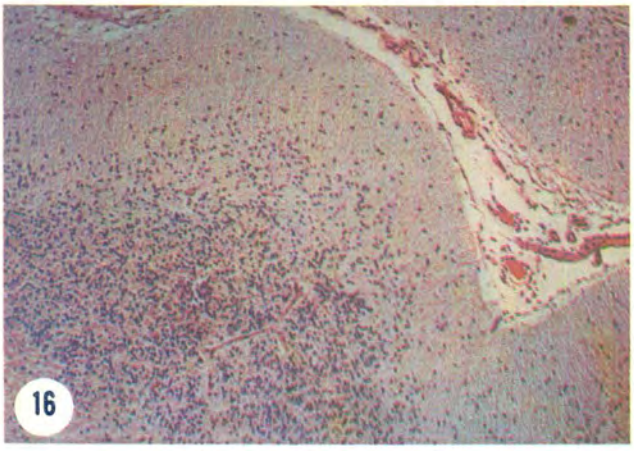
Tinctorial changes were obvious in these cells and no Nissl bodies were visible in the non-vacuolated parts of the cytoplasm, which stained strongly eosinophilic. Towards the periphery of the vacuolated areas the vacuoles were bigger and more irregular in outline,











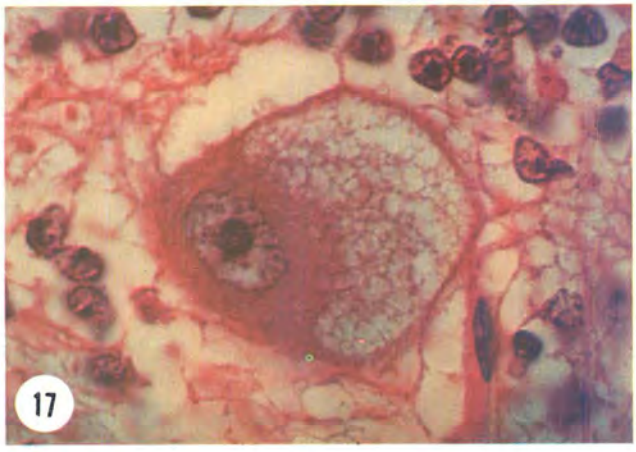


FIG. 12 Atrophy of cerebellar cortex in a natural case (right), compared to a normal brain (left)

FIG. 13 Atrophy of cerebellar cortex in an experimental case, Calf 1 (left) compared to a control brain (right)

FIG. 14 Coronal sections of the cerebellum of a natural case, showing atrophy of some folia

FIG. 15 Lower magnification picture of cerebellar cortex. Note complete absence of Purkinje cells. H.E. ×40

FIG. 16 Proliferation of glial elements in molecular layer and absence of Purkinje cells. The granular layer shows a decrease in cellular density. H.E. ×60

FIG. 17 A Purkinje cell with numerous vacuoles in its cytoplasm. H.E. ×500

while those closer to the non-vacuolated areas, usually around the nucleus, were smaller and more even in size.

Eccentric nuclei, situated away from the vacuolated part of the cytoplasm, were regularly seen in the partially vacuolated cells (Fig. 17). Many cells contained pyknotic or karyorrhectic nuclei, or showed chromatolysis. "Ghost forms", which still retained the general outline of Purkinje cells but in which the nuclei had disappeared and all cytoplasmic detail was lost, were frequently encountered. An eosinophilic, foamlike material represented the cytoplasm in these cells which sometimes also contained one or more very large vacuoles. A well-defined, thin eosinophilic band of cytoplasm surrounded the periphery of the vacuolated areas of the cytoplasm. The axons and dendrites of some of the affected cells seemed to be thickened.

In the less severely affected folia, a varying number of normal looking Purkinje cells were present among the many vacuolated ones, whereas folia were encountered in some of the long-standing natural cases with no Purkinje cells at all, or only an odd one here and there with a normal appearance.

Both the molecular and granular layers of the cerebellar cortex were diminished in thickness and, at the same time, the granular layer showed a decrease in cellular density. Proliferation of glia cells, occurring at the level of the Purkinje cells, also extended irregularly into the molecular layer and was most marked where Purkinje cells had disappeared (Fig. 16).

The white matter in the immediate vicinity of the cerebellar nuclei showed mild microcavitation, a diffuse increase of glial elements and some proliferation of capillaries. An occasional blood vessel in this region, as well as in the white substance of the folia and, less frequently, in the meninges, had a cuff of round cells. Vacuolated neurones were also encountered in the cerebellar nuclei, in nuclei in the peduncles of the cerebellum, the midbrain, thalamus, medulla oblongata and in neurones in the ventral horns of the spinal cord. The number of neurones affected varied from 1 or 2 to almost all in a particular nucleus. Where many neurones were vacuolated, varying degrees of gliosis occurred in the nuclei. Only odd neurones in the cerebral cortex showed vacuolation.

The vacuoles in the neurones were not stained by any of the histochemical procedures used.

Discussion

The clinical signs and lesions in the CNS, produced in the experimental animals fed with *S. kwebense*, were indistinguishable from those present in natural cases of maldronksiekte. These findings prove conclusively that maldronksiekte is caused by the ingestion of *S. kwebense*.

A vacuolar degeneration of neurones resulting in the death of these cells, and eventually atrophy of the cerebellar cortex, are the main pathological features of this disease. Although found in various parts of the CNS, the vacuolar degeneration of neurones was most prominent and widespread in the Purkinje cells of the cerebellum. All the cases studied as a whole give a general picture of the various stages in the development of the neuronal lesion. The initial change is a variation in the staining capacity of the cells, with localized vacuolation in some areas of the cytoplasm. This is followed by complete vacuolation of the cytoplasm, marked swelling of the cell and nuclear death. Necrotic neurones disappear and are replaced by glial proliferations. The disappearance of these neurones, together with a diminution of the cells in the granular layer, result in a reduction of the total mass of the cerebellar cortex.

The clinical signs in maldronksiekte clearly indicate some disruption of cerebellar function. The cerebellum is a central control point in the CNS for the organization of movement (Llinas, 1975). Diseases of the cerebellum usually disrupt the harmonious action of synergic muscle groups. Because of the complex, inter-dependent pathways of the CNS and the fact that vacuolar degeneration of neurones also occurred in other parts of the brain and spinal cord, the clinical signs in maldronksiekte probably cannot be ascribed to cerebellar damage only. In both natural and experimental cases, the clinical signs diminished in intensity after a time when the animals were exposed to daily handling. This phenomenon could be due to functional compensation, though compensation has never been observed in free-ranging affected cattle.

From Fig. 1 it can be seen that *S. kwebense* is fairly widespread over the northern parts of southern Africa. Up to now, however, the disease has only occurred on a limited number of farms in the Rooibokkraal area. One of the reasons for the localized occurrence of maldronksiekte is probably that this plant is not normally grazed in significant quantities when sufficient other food is available. Camps with a high incidence of the disease showed a severely disturbed vegetation as a result of continuous overgrazing. In these overgrazed camps the main grass, growing in the open sun away from the shade of trees, was *E. rigidior*, which is unpalatable and has a very low nutritional value. Furthermore the highly palatable and nutritious grass, *P. maximum*, normally restricted to shady areas under the trees, was completely replaced by thick stands of *S. kwebense*. The latter is a perennial which may reach an age of 6–8 years. Once *S. kwebense* becomes established no grass will grow in its vicinity, with the result that the animals are forced to feed on it.

Under certain conditions many species in the family Solanaceae are toxic to man and animals, the toxicity being mainly due to toxic principles which fall into the nicotine, atropine and solanine groups (Clarke & Clarke, 1970). The genus *Solanum* consists of about 1 500 species with a world-wide distribution, and poisoning is generally due to the presence of solanine (Kingsbury, 1964). This glycoalkaloid yields the sugar solanose and the steroid alkaloid, solanidine on hydrolysis (Clarke & Clarke, 1970). Solanine, however, is not the only active principle which has been isolated from this genus. Watt & Breyer-Brandwijk (1962) listed a variety of other chemical substances present in various species. Kingsbury (1964) pointed out that, despite the ancient and general reputation of members of this family being poisonous, very few feeding experiments have been performed with any of the toxic species. Acute solanine-like poisoning almost always occurs which is associated with the well-known clinical signs of apathy, drowsiness, salivation, dyspnoea, trembling, progressive weakness followed by paralysis and unconsciousness. The effects of gastro-intestinal irritation may include anorexia, nausea, abdominal pain, vomition and constipation or diarrhoea (Steyn, 1949; Kingsbury, 1964). These clinical signs were never observed, however, in the experimental or

natural cases in the present study. Maldronksiekte is a chronic intoxication with a latent period of at least 50 days between ingestion of the plant and the appearance of typical clinical signs.

Chronic poisoning with *Solanum* spp. have been reported in the literature in a few instances. Cattle chronically poisoned with *S. carolinense* showed emaciation, rough coat, anorexia, constipation and ascites (Kingsbury, 1964). Icterus has been associated with subacute poisoning by *S. carolinense* (Kingsbury, 1964) and *S. elaeagnifolium* (Buck, Dollahite & Allen, 1960; Kingsbury, 1964). *S. malacoxylon* has recently been shown to give rise to a form of bovine arteriosclerosis in South America. Metastatic calcification is seen in the endocardium, aorta and major arteries and various other organs, such as the lungs, kidneys and tendons (Döbereiner, Tokarnia, Da Costa, Campos & Dayrell, 1971).

Vacuolation of neurones has been described in various of the storage diseases in man and animals. These diseases are grouped under the name lipodystrophies or cerebral lipidoses and are due to errors in metabolism considered to have been inherited by means of recessive genes in man. Very few instances of lipidoses have been reported in the veterinary literature. The material within the vacuoles can readily be identified histochemically as lipid in nature, e.g. gangliosides and sphingomyelin (Blakemore & Palmer, 1971). In many lipidoses, an identical substance also accumulate in cells of the reticulo-endothelial system. Whittem & Walker (1957) reported a condition in Aberdeen Angus cattle which they labelled pseudolipidosis because of its histological resemblance to the lipidoses. There is no abnormality of lipid metabolism in this disease, however, and no lipid material can be demonstrated in the vacuoles. Vacuolation also occurred in renal tubular epithelium, macrophages of the lymph nodes and in cells of the thyroid and pancreas. Pseudolipidosis in Aberdeen Angus cattle is due to an absolute deficiency of α-mannosidase and the disease is inherited as a recessive (Blakemore & Palmer, 1971).

Laws & Anson (1968) reported vacuolation of the cytoplasm in neurones throughout the central nervous system in sheep grazing on *Swainsona luteola* and *S. galegifolia* in Australia. Vacuoles were also demonstrated in the epithelium of the convoluted tubules of the kidneys, the cytoplasm of reticulo-endothelial cells of lymph nodes and in the cytoplasm of the neurones of autonomic ganglia. The chemical nature of the material in the vacuoles was not determined. Lesions almost identical to those seen in natural cases in sheep were produced with *S. galegifolia* experimentally in the guinea-pig by Huxtable (1969). An ultra-structural study (Huxtable, 1970) showed that the vacuoles were single membrane-bound and that they had no clear-cut morphological relationship with the normal organelles.

Locoweed poisoning in live-stock in the United States of America is another plant toxicosis in which vacuolar degeneration of various cells in the body is a characteristic lesion. Oehme, Bailie & Hubert (1968) reported vacuolar changes of neurones in horses poisoned under field conditions. Van Kampen & James (1969) reproduced cytoplasmic vacuolar degeneration in neurones of the CNS, in the plexus of Auerbach and Meissner, reticulo-endothelial, liver, kidney and other cells of parenchymatous organs in sheep with 3 locoweeds, *Oxytropus sericea, Astragalus pubentissimus* and *A. lentiginosus*. The contents of the vacuoles were not determined.

The nature of the vacuolar degeneration of neurones in maldronksiekte as observed by light-microscopy is not clear at this stage. Electron-microscopic studies may assist in the exact characterization of this pathological change.

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