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LEUCOENCEPHALOPATHY IN MINK

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In human medicine, leucoencephalopathy is a term generally applied to a well-known infantile disease which appears in certain families. It is characterized by a general disturbance of the synthesis of the myelin sheaths as well as by a decomposition of the myelin sheaths already formed in the central nervous system (*Sperry & Waelsch* 1950). The disease is well-known in man and is considered to be a form of the so-called "diffuse sclerosis", or Schilder's disease (*Schilder* 1912) which, on the basis of histological and histochemical investigations, may be divided into several groups (*Christensen et al.* 1961; *Greenfield et al.* 1958). *Frauchiger & Fankhauser* (1957) indicate that no disease in animals is proved to belong to the true leucoencephalopathy. However, a similar disease has been reported in monkeys but is hardly ever seen in other wild animals (cit. *Fankhauser* 1961).

CLINIC

The leucoencephalopathy described in the following was demonstrated in standard minks from a mink herd with 800 breeding females. The disease was first noted in 1961. In the last part of 1962 and in 1963 the minks were further controlled to determine the nature of the disease.

According to information from the owner of the minks, the disease was hereditary. In 1963, however, it was noted that at birth the kits were normal, and that the clinical symptoms appeared later. Table 1 shows that the first signs of disease appeared when the kits were between 40 and 120 days old. When several kits in a litter were attacked, the disease appeared in all the kits at the same age. The earliest symptom was tremor when the kits

were startled. The tremor was universal, but most pronounced in the head so that the animal was unable to control the movement of the head. As tremor developed further the kits frequently fell over on one side. At a later stage they were unable to walk normally and finally became paralyzed. Paralysis was slightly more pronounced in the hind than in the fore extremities. A clinical evaluation of symptoms is given in the right column of Table 1. In this column, I designates the first stage in which

Table 1. Data of diseased animals.

Father no.	Mother no.	Kit no.	Kit sex	Date of birth	Disease observed	Death	Clinical symptoms at death
437 (1)	387 (?)	113	F.	4/5-62		*)14/9 -62	
493 (1)	404 (2)	203	M.	2/5-62		*) ?/10-62	
106 (1)	117 (1)	460	F.	3/5-62	?/9-62	?-62	
150 (3)	1440 (1)	677	M.	28/4-62		9/9 -62	
150 (3)	1440 (1)	678	F.	28/4-62		28/7 -62	
150 (3)	281 (1)	695	M.	6/5-62		*) ?/10-62	
150 (3)	281 (1)	699	F.	6/5-62		*) ?/10-62	
150 (3)	326 (1)	707	M.	2/5-62		*)14/9 -62	
150 (3)	326 (1)	708	F.	2/5-62		*)14/9 -62	
150 (3)	326 (1)	709	F.	2/5-62		1/9 -62	
150 (3)	326 (1)	710	F.	2/5-62		*) 6/9 -62	
151 (2)	1322 (1)	774	F.	6/5-62		*)19/11-62	II
151 (2)	149 (1)	782	F.	27/4-62		*)19/11-62	III
151 (2)	339(1+3)	786	M.	6/5-62		*)19/11-62	II
153(1+2)	1474 (1)	831	M.	3/5-62		22/9 -62	
153(1+2)	161 (1)	841	F.	30/4-62		16/10-62	
483 (1)	485 (1)	141	F.	2/5-63	16/8-63	*)11/9 -63	I
118 (1)	401 (2)	479	M.	3/5-63	15/6-63	*)11/9 -63	III
118 (1)	401 (2)	480	M.	3/5-63	15/6-63	9/9 -63	III
737(1+2+3)	621(1+2+3)	553	M.	2/5-63	5/7-63	*)11/9 -63	I
702(1+2)	619(1+2+3)	917	F.	2/5-63	27/8-63	*)11/9 -63	II
549 (3)	1394 (1)	2051	M.	28/4-63	1/7-63	11/9 -63	III
549 (3)	1394 (1)	2052	M.	28/4-63	1/7-63	*)11/9 -63	III
549 (3)	1394 (1)	2054	F.	28/4-63	1/7-63	*)11/9 -63	II
146(2+3)	1280 (1)	2077	F.	27/4-63	19/6-63	*)11/9 -63	III
146(2+3)	531 (1)	1101	F.	6/5-63	16/6-63	*)11/9 -63	I-II
146(2+3)	531 (1)	1102	F.	6/5-63	16/6-63	*)11/9 -63	II
798(1+2)	843 (1)	2175	M.	7/5-63	?/6-63	?/9 -63	III
798(1+2)	843 (1)	2176	F.	7/5-63	?/6-63	*)11/9 -63	III
796 (1)	770(1+2+3)	÷no.	F.	30/4-63	?/6-63	*)11/9 -63	III

(1): descended from male no. 1; (2): from male no. 2; (3): from female no. 3 (see text).
*) sacrificed.

tremor was observable among the kits, II the stage in which the kits were paretic and III the stage of paralysis. During the development of the disease the intake of food and water decreased. This caused weakness and finally cachexia. Most of the animals were killed before the weakness became extreme. Defecation and urination were normal, and the sensibility of the animals remained apparently unchanged.

As seen from Table 1, there were variations in the duration of the disease. In most instances the attack was of a subacute nature. None of the minks died before 2 months after the disease had been diagnosed. Some of the minks were not killed before November, the normal time for pelting.

PATHOLOGICAL ANATOMY

Macroscopic post mortem examination revealed no deviation from the normal. In the microscopic examination, changes in the central nervous system were found to be pronounced. Histological investigations were then made of various parts of the *cerebrum* as well as on the *cerebellum, medulla oblongata* and on *intumescentia cranialis et caudalis*. The tissue was imbedded in paraffin and sections were stained according to the following methods: van Gieson-Hansen, hematoxylin-eosin, Loyez (myelin sheaths), Romanes (neurofibrils), Einarson's gallocyanin (nucleo-proteins) as well as PAS. On frozen sections the following methods were used: Sudan III, Sudan black, Penfield's oligodendroglia stain, cresyl violet and the toluidine blue stain.

Histological examination revealed pronounced changes in the white matter in the *cerebrum, cerebellum, medulla oblongata*, and the entire *medulla spinalis*. Microscopic investigations were made of minks which, prior to killing, had shown symptoms corresponding to those observed during the 3 earlier cited stages in the development of the disease. By these investigations it was demonstrated that the pathological changes were of practically the same extent in all the minks investigated. However, the changes which occurred in the first stages of the disease were most pronounced in the cerebellum and this corresponded to other clinical symptoms such as disturbances of balance.

Whereas the grey matter, apart from slight edema, seemed to be normal, changes were everywhere present in the white matter in the form of typical degeneration of the myelin sheaths (Figures

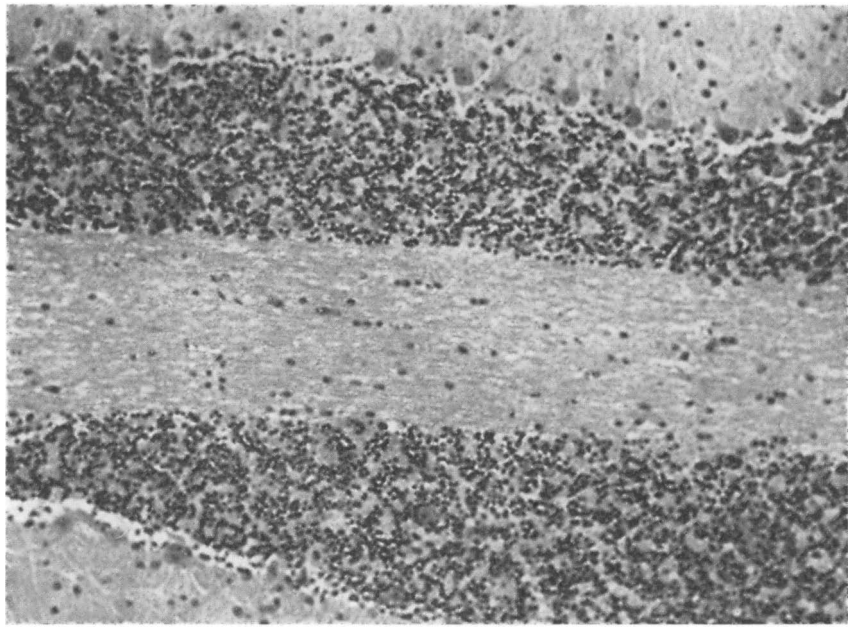

Figure 1. Cerebellar folium from normal mink. Hematoxylin-eosin (magn. appr. 140 ×).

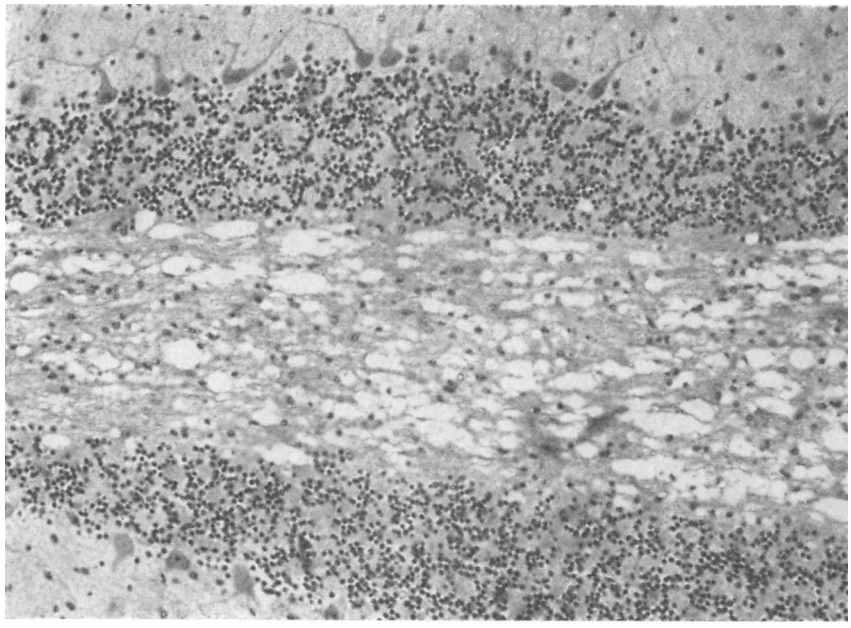

Figure 2. Cerebellar folium showing vacuolated degeneration of the white matter. Hematoxylin-eosin (magn. appr. 140 ×).

1 and 2). Ganglion cells and the axiscylinders were only slightly swollen, but there was pronounced degeneration of the oligodendroglial cells as well as insufficient myelination and degeneration of already myelinized regions of the white matter. In cases where the disease was in its last stages, there was pronounced proliferation of astrocytes in the totally demyelinated white substance. Located perivascularly were moderate cell infiltrations (Figures 3 and 4) consisting of macrophages, which by fat staining of frozen section, were found to contain material which was sudanophilic. It was further possible to demonstrate a moderate quantity of PAS positive substance, although no other positive PAS reaction was found in the injured tissue. By staining with cresyl violet and toluidine blue, pronounced metachromasia was observed in the demyelinated areas. Large cells were present containing brown substance in cresyl violet staining and reddish substance in toluidine blue stained sections. As the histological findings indicate, the diagnosis of this disease must be leucoencephalopathy.

ETIOLOGY AND DISCUSSION

As already stated, the leucoencephalopathy described here was recorded from a single mink herd, and there, only on standard mink. The majority of these minks were descendants of animals purchased abroad. Among these, a single male, No. 1, and its progeny have been used frequently in breeding since 1958. As shown in Tables 1 and 2, in 1962 leucoencephalopathy was found in 16 minks from 11 litters, and in 1963, in 14 minks from 9 litters. The descent of the 20 parent pairs of minks could be traced back on both the father's and mother's sides to the already mentioned male mink No. 1, or to a male mink, No. 2, imported at the same time, or in certain cases, to a female, No. 3, littermate to mink, No. 1. The only exception was in one case where none of the above-mentioned minks were to be found in the ancestry of the mink mother. Here it should be stated that on a mink farm, with such a large number of minks, it is possible, in spite of careful control, that an interchange of minks may occur, or a non-registered mating take place. The common descent from these 3 minks suggests, plainly, that the disease is hereditary. In that case it must be due to a recessive, sub-lethal factor, and since the disease was not found in the parents of the minks attacked, the possibility of a dominant inheritance is excluded. As

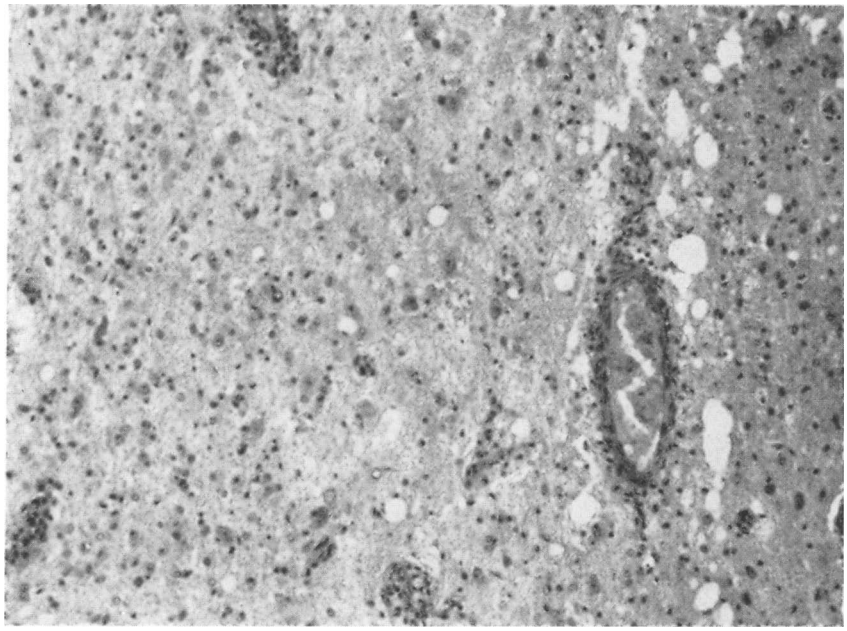

Figure 3. Semioval center of cerebral hemisphere. Perivascular cell-infiltration, vacuolation of the white substance and micro-glial cell-proliferation are visible. Hematoxylin-eosin (magn. appr. 140 ×).

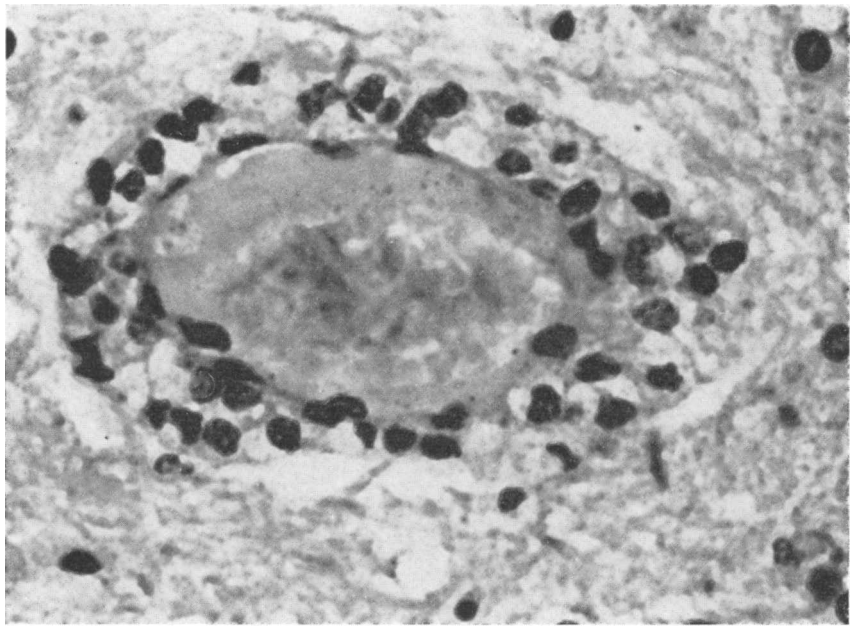

Figure 4. Perivascularly arranged macrophages in degenerated white matter. Hematoxylin-eosin (magn. appr. 860 ×).

the material available was rather small, it is impossible to demonstrate with complete certainty that a simple, recessive inheritance is the cause.

However, the distribution for the two years shows no significant deviation from an expected 3:1 segregation (Table 3). The disease appeared in both male and female kits (Table 2) and was equally distributed among the two sexes. In both Table 1 and Table 2 it is apparent that in general only one or two kits from a litter were attacked by the disease. This also indicates that we are dealing with an autosomal, recessive factor.

In minks, the disease which from differentially diagnostic viewpoint may first come under consideration is thiamine deficiency (*Ender & Helgebostad* 1939; *Leoschke & Elvehjem*

T a b l e 2. Distribution of normal and attacked male and female kits.

	Mother no.	Number of kits					
		normal		affected		total	
		males	females	males	females	males	females
	387	1	2	0	1	1	3
	404	0	3	1	0	1	3
	117	0	2	0	1	0	3
	1440	0	1	1	1	1	2
	281	3	1	1	1	4	2
1962	326	0	0	1	3	1	3
	1322	1	2	0	1	1	3
	149	5	1	0	1	5	2
	339	3	2	1	0	4	2
	1474	2	3	1	0	3	3
	161	0	3	0	1	0	4
Total	11	15	20	6	10	21	30
	485	2	2	0	1	2	3
	401	2	3	2	0	4	3
	621	1	2	1	0	2	2
	619	1	3	0	1	1	4
1963	1394	0	2	2	1	2	3
	1280	2	2	0	1	2	3
	531	2	1	0	2	2	3
	843	0	1	1	1	1	2
	770	0	2	0	1	0	3
Total	9	10	18	6	8	16	26

Table 3. Distribution of normal and diseased animals.

	Number of kits		
	total	normal	affected
1962	51	35	16
1963	42	28	14
1962 + 1963	93	63	30
Expected		69 3/4	23 1/4
$\chi^2 = 2.29$	$0.1 < P < 0.2$		

1959). This disease, well-known also as *Chastek*'s paralysis in foxes, is due either to insufficient thiamine supplementation, or to the presence of thiamine destroying enzymes in the diet. Clinically the disease is characterized by nervous symptoms, convulsions or paralysis. Furthermore the appetite of the affected animals is considerably reduced. Thiamine deficiency has been observed from time to time in the herd in question and treatment with thiamine gave curative or preventive results. On the other hand, the application of thiamine had no effect on the diseased animals in question. Furthermore, histopathological observations in cases of pronounced lack of thiamine, deviate very considerably from those described above, in that thiamine deficiency causes, for example, widespread hæmorrhages which are macroscopically demonstrable, in the grey matter of the brain (*Innes & Saunders* 1962). *Chastek*'s paralysis is frequently compared, both from the viewpoint of etiology and of changes in the brain, with the so-called *Wernickes* disease in man (*Evans et al.* 1942; *Frauchiger & Fankhauser* 1957).

As already stated, leucoencephalopathy is a well-known disease in man and a thorough classification of the disease into groups has been made by many research workers. Thus it has been possible to subdivide it into 3 groups (*Christensen et al.* 1961): I *Krabbe*'s form, also called the globoid cell type. II The *Pelizæus-Merzbacher* type. III The *metachromatic* type. These types are characterized not only by their different histological manifestations, but also by their pathogenetic and ethiological variations (*Lhermitte* 1950). With the exception of a more unusual sub-group of the metachromatic type, which appears sporadically in adults, these three forms of leucoencephalophaty

occur most frequently in infancy or later in childhood. They are common in certain families and are presumably all due to a congenital metabolic anomaly of a nature not yet elucidated (*Edgar* 1957).

A comparison of the histological changes which appear in children and in mink kits indicates that the leucoencephalopathy in mink resembles the metachromatic form of leucodystrophy in man (*Hirsch & Pfeiffer* 1957; *Diezel & Richardson* 1957). Clinically, this disease appears in the child at somewhat different times during the first years of the child's life and results in death after a duration of 1 to 2 years. In spite of the difficulty in comparing the stage of development, it seems as though the disease appears at nearly the same "biological" age in children and in mink kits. In man the etiology of this disease is far from being clear, but the histological changes indicate enzymatic disturbances at one or more points in the proteo-lipid metabolism. As already stated, the degenerative changes are characterized for example by the metachromatic staining reactions, which are presumed to be due to an abnormal accumulation of pre-lipids together with cerebrosides combined with sulphuric acid (*Diezel* 1955). A neuro-pathological comparison with the human cases will be published (*Christensen & Palludan* 1965).

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REFERENCES

Christensen, E., Melchior, J. C. & Negri, S.: A comparative study of 16 cases of diffuse sclerosis with special reference to the histopathological findings. Acta neurol. scand. 1961, *37*, 163—207.

Christensen, E. & Palludan, B.: Acta Neuropathologica, 1965, in press.

Diezel, P. B.: Histochemische Untersuchungen an den Globoidzellen der familiären infantilen diffusen Sklerose vom Typus Krabbe. Virchows Arch. path. Anat. 1955, *327*, 206—228.

Diezel, P. B. & Richardson, E. P. jr.: Histochemical and neuropathological studies in leucodystrophy. J. Neuropath. exp. Neurol. 1957, *16*, 130—131.

Edgar, G. W. F.: Leuco-dystrophy as an "inborn metabolic error" comparable to lipidosis. Cerebral Lipidoses. A Symposium. Blackwell Scientific Publications, Oxford 1957, 186—195.

Ender, F. & Helgebostad, A.: Eksperimentell beriberi hos sölvrev. Skand. Vet.-Tidskr. 1939, *20*, 1232—1244.

Evans, C. A., Carlson, W. E. & Green, R. G.: The pathology of Chastek paralysis in foxes. Amer. J. Path. 1942, *18*, 79—92.

Fankhauser, R.: Neuropathologic observations in wild animals. World Neurology 1961, *2*, 2—12.

Frauchiger, E. & Fankhauser,, R.: Vergleichende Neuropathologie des Menschen und der Tiere. Springer Verlag, Berlin 1957, 451.

Greenfield, J. G., Blackwood, W., McMenemey, W. H., Meyer, A. & Norman, R. M.: In: Neuropathology. Demyelinating diseases. London 1958, 441—474.

Hirsch, Th. V. & Peiffer, J.: A histochemical study of the pre-lipid and metachromatic degenerative products in leucodystrophy. Cerebral Lipidoses. A Symposium. Blackwell Scientific Publications, Oxford 1957, 68—76.

Innes, J. R. M. & Saunders, L. Z.: Comparative Neuropathology. Academic Press, 1962, 839.

Leoschke, W. L. & Elvehjem, C. A.: The thiamine requirement of the mink for growth and for development. J. Nutr. 1959, *69*, 211—213.

Lhermitte, F.: Les leuco-encéphalites. Editions Med. Flammarion, Paris, 1950, 263.

Schilder, P.: Zur Kenntnis der sogenannter diffusen Sklerose. Z. ges. Neurol. Psychiat. 1912, *10*, 1—60.

Sperry, W. M. & Waelsch, H.: The chemistry of myelination and demyelination. In: Multiple sclerosis and the demyelinating diseases. Williams and Wilkins Co. Baltimore 1950, 255—267.

SUMMARY

In a herd of standard minks 30 cases of leucoencephalopathy were demonstrated in the mink kits in the years 1962 and 1963. The disease is assumed to be hereditary and due to a sub-lethal, recessive, autosomal factor. A comparison with the forms of diffuse sclerosis found in man demonstrated that the disease, as it appeared in minks, bore a striking resemblance to the so-called metachromatic type of leucoencephalopathy.

ZUSAMMENFASSUNG

Leukoencephalopathie beim Nerz.

In einem Bestand von Standardnerzen wurden in den Jahren 1962 und 1963 insgesamt 30 Fälle der Leukoencephalopathie bei Nerzjungen festgestellt. Es wird angenommen, dass das Leiden erblich bedingt ist und von einem subletalen, rezessiven, autosomalen Faktor herrührt. Ein Vergleich mit den human vorkommenden Formen der diffusen Sklerose zeigte, dass das Leiden, welches beim Nerz festgestellt wurde, dem sogenannten metachromatischen Typ der Leukoencephalopathie sehr ähnlich war.

SAMMENDRAG

Leukoencefalopati hos mink.

I en besætning af standardmink blev der i årene 1962 og 1963 ialt påvist 30 tilfælde af leukoencefalopati hos minkhvalpe. Lidelsen antages at være arveligt betinget og skyldes en subletal, recessiv, autosomal faktor. Ved sammenligning med de humant forekommende former af diffus sklerose havde den hos minkene påviste lidelse stor lighed med den såkaldte metakromatiske type af leukoencefalopati.

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