



Research report

The early history of the transmissible spongiform encephalopathies exemplified by scrapie

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ABSTRACT

Transmissible spongiform encephalopathies (TSE) is a group of diseases that is unique in comprising disorders that can occur sporadically, are hereditary and/or infectious. The transmissible pathogen – the prion – is distinct from all other pathogens in being devoid of nucleic acids.

During the elucidation of these disorders, many different – and contradictory – theories have been put forward. Early researchers, mostly driven by the economic impact of these diseases on sheep farming, engaged in heavy disputes concerning heredity vs. infectivity of scrapie. Following the experimental demonstration of scrapie's infectivity during the 20th century, research focused on the characterization of the nature of the transmissible agent.

The current work comprehensively summarizes the available early literature on TSE research. A review of the historical literature is presented, describing the efforts in breeding, transmission experiments, and theories about the nature of the infectious agent.

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1. Introduction

The term “transmissible spongiform encephalopathy (TSE)” is used to denote a group of inevitably fatal neurodegenerative disorders affecting mammals and man. TSEs affecting man include Creutzfeldt-Jakob-disease [43,98,99], Gerstmann-Sträussler-Scheinker-syndrome (GSS) [73,74], Kuru [72,204], fatal familial insomnia (FFI) [121] and sporadic fatal insomnia (sFI) [122,124]. TSEs affecting mammals are scrapie in sheep and goats, transmissible mink encephalopathy in mink (TME) [30,86], chronic wasting disease in elk, mule deer and white-tailed deer (CWD) [198], bovine spongiform encephalopathy in cattle (BSE, mad cow disease) [194], exotic ungulate encephalopathy in exotic ungulates (EUE) [100,102] and feline spongiform encephalopathy in cats (FSE) [115,201].

In earlier times, people most interested in scrapie were the sheep farmers who were directly affected by its economic impact. Since then, the interest in TSEs has broadened to the research community and – caused by BSE's pathogenic potential for humans – to

the general public, which can be recognized by scrapie's mention even in fiction [177,178].

During the 20th century, different theories on the nature of the causative agent of TSEs were put forward. In the course of time, most of these turned out to be unfounded. The TSE agent was proposed to be (in chronological order of publication):

- sarcosporidia (1914) [128];
- a filterable virus (1938) [45];
- a slow virus (1954) [170];
- a replicating polysaccharide (1966) [8,61];
- a protein (1967) [81,140];
- a replicating membrane (fragment) (1967) [75,94];
- a DNA-polysaccharide complex (1968) [3];
- a viroid (1972) [52];
- a lipid (1978) [10];
- a *Spiroplasma* sp. (1979) [18–20,78];
- a virino (1979) [51];
- a prion (1982) [146];
- a virus (1984) [123,157–159];
- mitochondria(1 nucleic acid(s)) (1989) [5,6];
- a holopron, consisting of PrP^{Sc} (PrP in the scrapie specific conformation, the apopron) and a (dispensable) nucleic acid (the copron) (1991) [193].

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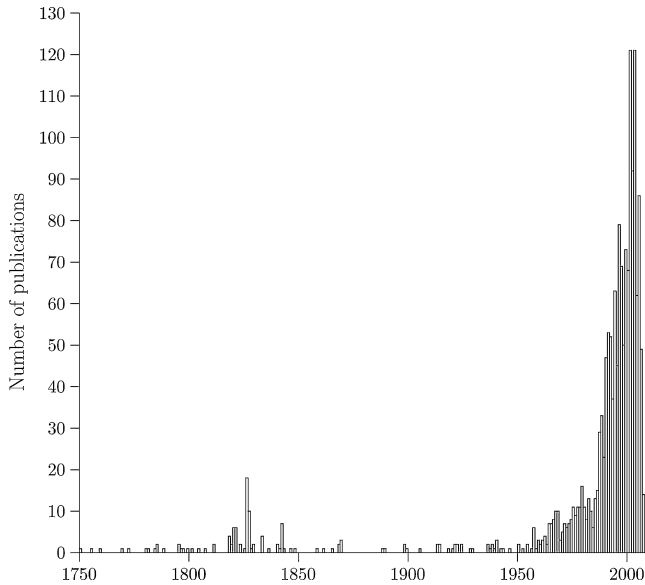


Fig. 1. Publications on transmissible spongiform encephalopathies (literature analysis with Index Medicus and cross citations; results are comparable to an analysis concerning CJD (1966–1985) [27].

The most popular propositions put forward for the causative agent were a virus and a pathogenic protein (the prion). Unusually long incubation periods militated against viruses as cause. These long incubation periods gave rise to the term ‘slow virus’. Infectious proteins, on the other hand, seemed to contradict a biochemical dogma stating that information coding the structure of proteins is exclusively derived from nucleic acids while proteins never code for amino acid sequences.

A chronological analysis of the published literature and the increase in the number of publications on TSEs reflect a progressive increase in interest in these disorders. Reasons for this increase are both findings and theories that were regarded as especially important as well as the economic impact [28] of the disease. The upsurge in the number of publications after the middle of the 20th century coincides with an idea stated by Hadlow [84] in 1959: two diseases so far considered unrelated might have a common cause – scrapie in sheep and kuru, which was described in 1957 for the first time, in the Fore (aborigines in Papua New Guinea). This idea launched a still continuing research boom. The increase in publications was accelerated in 1985 by the advent of the bovine spongiform encephalopathy which, originating in UK, necessitated the culling of hundreds of thousands of cattle. The paramount economic impact of this disease is reflected in the funding mobilized primarily for the elucidation of its cause as well as for its prevention (74 projects funded in Germany as of December 2007,¹ 55 projects funded by the EU,² 35 projects funded by the U. S. Department of Agriculture³). The amount of research results is directly recognizable in the number of publications. As far back as 160 years, there was – for former circumstances – a comparable rise in publications, driven by enormous losses caused by an increased number of scrapie cases in many areas of East Germany (see Fig. 1). The decline in publications (in the last few years), visible in the figure, is caused by the way the literature was collected – by tracking citations.

The uncertainty concerning the origin of TSEs that was prevalent until the 1990s and the still persisting uncertainty concerning the mode of transmission of some naturally occurring TSEs has a long history that dates back to the first descriptions of scrapie more than 250 years ago.

Considering the popularity that TSEs have achieved in recent years, there are remarkably few publications focussing on the historical development of TSE research [28,85]. Most of them are introductory chapters of books [4,91,137,196].

This paper presents an analysis of publications on scrapie during the period from 1750 until 1936. This period starts with the first publication describing scrapie [118] (see Fig. 2) that is still reliably trackable. The end of this period is the year in which Cuillé and Chelle [44] demonstrated without any doubt scrapie to be transmissible.

After a short quantitative and qualitative literature review, the article concentrates on historical attempts to transmit scrapie. After discussing the impact of breeding on scrapie, it focuses on the pitfalls of transmission experiments and finally presents different theories about the character of the transmissible agent of scrapie.

2. Historical literature

Scrapie is the disease with the longest history of publications and the prototype of TSEs. The analyzed publications comprise original articles, reviews and contributions to periodicals. Almost all authors were devoted to the search for the cause of the disease. The multitude of proposed causes is by all means comparable to the number of suggested pathogens put forward during the 20th century.

Some publications refer to a paper dating back to the year 1732 as the first description of scrapie. However, this is considered to be a misconception because a publication from this year cannot be found. At the same time, in 1772, scrapie was reported to be known for some 40 years – a point in time dating back to the year 1732:

This Distemper is generally said to be of about forty Years standing in England . . . [40]

There are several other references pointing to years before 1750. Gajdusek claims that the first citations are from the 17th century [69]. Brown [26] mentions first reports dating back to the 15th century. Gaiger [68] presumably and May [126] explicitly refer to Kuers [111] who mentions a reference by an agricultural writer at the time of the Romans. All of these authors unfortunately failed to supply the corresponding citation.

The analyzed literature (predominantly German – reflecting the geographical focus of the disease as well as the availability of the literature) was mostly written by “Ökonomen” (economists). These “Ökonomen” were shepherds, farmers, or their – often aristocratic or governmental – employers. Reports written by veterinarians and natural scientists are scarce, in part because the disease was not known to them:

Scrapie has been known for a long time, being put on record by several agricultural authors. Moreover, old shepherds know it. Only veterinarians missed this disease [180].⁴

This remarkable situation is explainable by the attempt of many shepherds to keep the breakout of scrapie in their herds secret [188]:

¹ http://www.tse-forum.de/tse_forum/index_eng.htm.

² <http://cordis.europa.eu/search/index.cfm?fuseaction=proj.resultslist&CFID=19509078&CFTOKEN=408622>.

³ <http://cris.csrees.usda.gov/>.

⁴ [Scrapie] ist . . . längst bekannt gewesen, – nur nicht den Thierärzten – ihrer ökonomischen Schriftstellern erwähnt, auch kennen sie alte Schäfer [180].

Von denen mancherley Krankheiten des Schaafviehes, und was vor Curen damit vorgenommen werden.

Der Trab ist auch eine Krankheit der Schaaf, und ist ansteckend. Es bekommen auch manche Schaaf den Trab, welches eine Krankheit ist, die daran zu erkennen, wenn sich das Stücke, das solchen bekommt, niederleget, und beißet mit dem Maule an den Füßen und um die Weine, und reiben sich mit dem Kreuze an denen Stangen, verlieren das Gedeyen, freßen auch nicht recht, und verlahmen endlich; sie schleppen sich lange, verzehren sich nach und nach, und zuletzt müssen sie sterben. Welches Vieh diese Staup bekommt, wird nicht besser. Daher denn das allerbeste ist, daß ein Schäfer, welcher ein Stücke von dem Trabe befallen, gewahr wird, es balde wegschafft, und vors Herrschafftliche Gefinde schlachtet. Es muß ein Schäfer ein solches Stücke Vieh also gleich von dem gesunden Vieh absondern, denn es steckt an, und kan vielen Schaden unter der Heerde verursachen.

Source: Johann George Leopoldt (1750): Nützliche und auf die Erfahrung gegründete Einleitung zu der Land-Wirthschaft, Part 5, Chapter 12, p. 348. Sorau [118].

For its historical importance the text shall be reproduced here in present-day English:

About the various illnesses of sheep and the treatments that are applied

Occasionally, some sheep contract scrapie, an illness recognizable in the recumbency of the animal. It nibbles at its claws and feet and scratches its back against posts. It ceases to prosper, loses appetite and finally gets weary. They drag themselves for a long time, are consumed more and more, and in the end, they are doomed to death. Animals that fall ill with this distemper won't recover. Therefore, the very best a shepherd can do who has caught sight of an animal that has fallen ill with scrapie, is to cull the animal and slaughter it for the noblemen's servants. Thus, it is advisable for a shepherd to immediately separate such an animal from the healthy life-stock, as this disease is contagious and can cause great damage to the flock.

Fig. 2. First mention of scrapie.

Every single beauty of the body, every exceptional feature of the wool of the sires will be stressed as much as possible. All abnormalities of the herd will be hidden from the eye of the buyer. Individuals only raising the vague suspicion of being affected by scrapie will *never ever* be showcased to the scrutinizing inspection of the knowledgeable [1].⁵

M'Gowan characterized this behaviour of the shepherds as "*suppressio* at least, if not a *perversio veri*" [128].

The lack of awareness of scrapie by veterinarians may be one reason why neither genetics (around 1860), nor bacteriology (around 1880) had any impact on the elucidation of scrapie's causes. It took until the end of the 1930s that scrapie's transmissibility was demonstrated beyond any doubt [44–47]. Moreover, although the earliest available description of scrapie [118] clearly states that the disease is infectious, during the 19th century there was a widespread conviction that the disease is transmitted by sexual intercourse (this view is found in more than half of the articles that were analyzed) and might have hampered the consideration of, and thus also the conduction of experiments analyzing any other mode of transmission (less than one fifth of the analyzed articles propose infection by mere coexistence of animals or spontaneous appearance of scrapie as a cause).

The literature can be subdivided into two groups:

- retrospective case and/or autopsy reports;
- contributions criticizing and comparing these case reports with each other (reviews).

There are lengthy discussions about the causes and the modes of transmission of scrapie. Many authors were convinced that the disease can develop spontaneously, an opinion partially substantiated by a reference to flawless biblical circumstances [164]. This idea, proposed in 1826, resembles the degeneration concept formulated shortly thereafter by Augustin Morel (1809–1875). Morel, too, assumed a biblical "type primitif", which was modified somatically, morally and psychically from generation to generation by external circumstances resulting in disease [165].

According to the medical concepts prevalent at the time, early reports about this disease discussed miasmata [147,190], thunder [156] or other exceptional atmospheric events [148–150], intoxication [25], worm infections [66], poor quality or insufficient amounts of food [126,162,163], too nourishing a pasture [65,66,88] or feedstuff [55,57,88,126,148,152,154], too humid a pasture [111] or too much humidity in the sheep pen [154], nutritional deficiencies in sodium or potassium salts [57], tail docking [126], too young [56] or too old [57,162,163] dams, too early [29,55,57,88,126,154,174,181], too late [88,164], too little [65,66,152,154,182] or too much [55,57,126,138,154,174] sexual activity of the rams, cross-breeding [55,154] or inbreeding [126] as possible causes of scrapie.

⁵ Jede Körperschönheit, jede vorzügliche Woll-Eigenschaft der Stähre wird nach Würden herausgestrichen, alle Abnormitäten der Heerde werden dem Auge des Käufers möglichst entrückt, und Individuen, die die Traberkrankheit nur ahnden lassen, dem prüfenden Blicke des Kenners bestimmt nicht und am allerwenigsten dargestellt [1].

Causal research was done using correlations, comparing affected with unaffected sheep farms. Different methods of care taking, atmospheric or other conditions prevalent in one but not in the other sheep farm were proposed as causative.

Despite some authors doubting scrapie's heredity [110], it was common sense by the end of the 18th [40] and in the beginning of the 19th [181,188,191] century that scrapie was a hereditary disease. Thaer, in 1826, described scrapie's mode of hereditary transmission as 'greater or less predisposition to acquire this disease in one or the other state of development if some additional circumstance would happen' [182].⁶

At that time, many authors held mostly the rams responsible for propagation of the disease during copulation [1], resulting in suggestions to control the spread of disease by mating only healthy rams with the ewes [138]. However, Thaer, in a comment to Rudolphi [161], as well as von Richthofen [189], conceded that scrapie can also show up without a hereditary predisposition, thereby affecting animals in hitherto healthy flocks. Beyond this, once the disease had developed spontaneously, it was considered to be henceforth hereditary, a proposition resembling Lamarck's ideas about the origin of hereditary traits formulated in 1809.

There were sporadic reports [129,162,163] referring to scrapie by one of its customary names and describing the symptoms correctly, but nevertheless suggesting that the affected animals recovered mostly with or without treatment.

Despite these dubious descriptions, the prevalent advice given to shepherds who noticed this disease among their sheep was to cull the entire flock [186] and to move the sheep to a different paddock. It might be supposed that the idea of breeding animals for resistance against scrapie by selecting supposedly less susceptible animals as a way to combat this torment gained additional impact with Darwin's ideas about evolution and Weissmann's germ plasm theory that neglected any Lamarckian concepts of the heritability of acquired characteristics. This idea of breeding sheep against susceptibility to scrapie is still up-to-date, given the correlation between genotype and susceptibility.

As early as 1821, when Richthofen called scrapie a hereditary malady ("Erbübel") [155], Albrecht Daniel Thaer [181] described a hereditary predisposition and a transmission of this disease by asymptomatic animals. The same author suspected a hereditary and a non-hereditary variant of scrapie to exist [188], which, admittedly, were found not to be discriminable by their symptoms. Further ancient references to the knowledge of a hereditary predisposition for scrapie, dating back to the years 1826 and 1827, respectively, can be found by Thaer [182] and by von Richthofen [188,191]. Von Richthofen calls scrapie a 'hereditary malady intended to distribute perpetually'⁷ and states 'that the ailment is not restricted locally, but shows up only if heredity or contagion were causally involved'⁸[191].

Despite the early knowledge of infectivity, there were several unsuccessful attempts to transmit scrapie, leading to doubts as to whether scrapie is indeed infectious. Dammann [48], in 1869, tried to transmit the disease from sheep to sheep by keeping healthy and diseased animals together in the same herd. After an observational period of up to 22 months, this experiment turned out to be

unsuccessful. Thereafter, he transferred blood of diseased animals to mucous membranes of healthy ones. Once again, transmission of scrapie was not achieved (no observation period was given). This led the author to speculate about a route of transmission through fly larvae, an experiment that succeeded only more than 130 years later [142]. Dammann consequently considered scrapie to be non-infectious.

Cassirer [32] adopted Dammann's view that scrapie is not an infectious disease. In 1898, he reported the examination of five sheep, one of them only post mortem, that had succumbed to scrapie. After having excluded insects found in the frontal sinus at necropsy, as well as cocci used in transmission experiments, as vectors of scrapie, he analyzed the central nervous system. Following gross anatomical as well as microscopic examinations, he concluded that, within the limitations of the methods available at his time, *the nervous system shows no modifications in scrapie diseased animals* (our italics). This is in clear contrast to Besnoit's [25] observations, who, in the same year, detected profound injuries of the nervous system and peripheral nerves, as well as obvious vacuolation. He proposed an intoxication of sheep, acquired from food, as the reason for disease.

Among the majority of authors, there was widespread agreement that changes in the spine of patients could be found [126], which were claimed to have been observed during necropsies. This might be explainable with the observed problems in locomotion. Many authors reported sheep in the late states of disease having difficulty following their flock.

Starting with an initial affection caused by one or the other agent, the authors described the transmission from patient to hitherto healthy flock fellows. During the discussions of possible transmission routes, a clear distinction between genetically transmitted and infectious disease was lacking. While there were reports about an infection of the mating partner or of the embryo during copulation, a distinction between genetically transmitted and sexually transmitted disease was not being made. Both, a transmission from ram to dam and from dam to ram was considered possible. However, the probability of contracting scrapie was reported to depend on gender (ram > ewe > wether) [126,152]. This confusion is recognizable in the following citation:

However, what is most important from the author's point of view for the persistence and distribution of scrapie is infection: plain infection as well as infection during copulation . . . [151]⁹

This passage is equally suited to describe an infectious as well as a sexually or genetically transmitted disease. Another citation from the same year but by another author highlights this intermingling:

There are two ways for this disease to spread. First, by copulation, in fact with greater probability by the male than by the female participant. Second, it is contagious by gregariousness of diseased and healthy animals in flocks, in sheep-pans and on the paddock. . . . First of all, the shepherd who is eager to rid his herd of the disease is advised to remove all sires – except those which have been proven not to be affected – and replace them with animals which are completely free of hereditary diseases [1].¹⁰

⁶ Jeder, der einen verständigen Begriff von Krankheit hatte, bezog das Erbliche nur auf eine größere oder geringere Disposition, diese Krankheit in einer gewissen Entwicklungsperiode zu bekommen, wenn irgend eine veranlassende Ursache hinzukäme, wie das bei vielen thierischen und menschlichen Krankheiten der Fall ist [182].

⁷ "... immer weiter sich verbreiten wollendes Erbübel" [191].

⁸ "... daß diese Krankheit keinesweges örtlich, sondern blos alsdenn entstanden sei, wenn die Erblichkeit oder Ansteckung dabei zum Grunde lag..." [191].

⁹ Dasjenige aber, worauf nach der Meinung des Herrn Verfassers das Bleiben und Verbreiten der Traberseuche am vorzüglichsten beruhet, ist die Ansteckung, sowohl an und für sich, als auch das Anstecken durch die Begattung . . . [151].

¹⁰ Ansteckend ist die Krankheit auf zwei Wegen. Erstlich durch die Begattung und zwar mehr durch den männlichen als durch den weiblichen Antheil. Zweitens wird sie ansteckend durch das Zusammenleben kranker und gesunder Thiere

Today, it is hard to conceive how to justify the requirement of absence of any hereditary disease in order to prevent an ailment that is supposed to spread by cohabitation.

The lacking distinction between the different modes of transmission, which was prevalent in the 19th century, was recognized by the beginning of the 20th century [173]. However, the depreciation of the idea of a disease that can be transmitted by infection as well as by genetic transmission was justified by the lack of any other disorder that unites both ways of transmission:

These observations I think justify the conclusion that the disease spreads by contagion. It has been stated by a considerable number of farmers that the disease is hereditary, and some have stated their belief that it is both hereditary and contagious. I may point out, however, that no disease is known which is both hereditary and contagious, although the mistake is not unnatural in a lay mind, which does not always distinguish between hereditary transmission and congenital infection [173].

The analysis of scrapie was complicated by the fact that in former times many other diseases affecting sheep (Drehkrankheit, Kreuzdrehe and Gnubberkrankheit) were confused with scrapie. Different authors considered one or more of them to be identical with or different from scrapie. Contemporary authors tried to discriminate “Drehkrankheit”, “Gnubberkrankheit”, “Kreuzdrehe” and “Traberkrankheit”. While many of them differentiated between “Drehkrankheit” and “Kreuzdrehe” on the one hand and “Traberkrankheit” on the other [57,66,88,111,126,153,161,180,191], there were other authors who considered “Kreuzdrehe” and “Traberkrankheit” to be the same, but to be different from “Gnubberkrankheit” [192]. Spinola [171], however, used the terms “Gnubberkrankheit” and “Kreuzdrehe” synonymously. This confusion of terms, as well as the vague and ambiguous description of the symptoms of scrapie and of the other diseases, hamper the attempt to extend scrapie’s documented history beyond the year 1750. What makes things worse are the many different names that were used to refer to scrapie (see Table 1).

3. Breeding

Since their domestication about 11,000 years ago [141], sheep have served different purposes as farm animals. They were and are used as suppliers of food (mutton and milk), clothing (fur and wool) and fertilizer. Strings of instruments can be made out of sheep gut, while percussion instruments can be manufactured using sheep skin. In recent times sheep are (together with goats) employed in landscape conservation. Complete man-made landscapes as the Lüneburger Heide (in Northern Germany) or the Rhön (low mountain range in the border triangle of Hesse, Thuringia and Bavaria (Germany)), are indeed inconceivable without sheep [166].

For millennia, man tried (and succeeded) to improve the quality of meat and wool as well as the amount of milk produced by sheep by selective breeding. During the middle ages, sheep of good wool quality were considered an asset worthy of protection. Aristocratic sheep owners, the Mesta, forbade exportation of Merino sheep from Spain on penalty of death [12]. This demonstrates the efforts invested in and the value of breeding sheep with desirable phenotypes.

in einem Haufen, in einem Stalle und auf einer Weide. ... Der Schaafzüchter, welcher seine Heerde von der Traberkrankheit ganz reinigen will, muß fürs erste alle gebrauchten Sprungböcke, wenn nicht Individuen darunter sind, deren Traberfreiheit unbezweifelbar erwiesen ist, fortschaffen, und muß ganz von erblichen Krankheiten freie sich zu verschaffen suchen [1].

Table 1

Historical/locally customary names of scrapie (in alphabetical order).

| Name of scrapie | Used in | Citations |
|---|------------------|--------------------------|
| Basquilla Disease | Spain | [190] |
| Cuddie Trot | Scotland | [87,120,128] |
| Drab(en) | Germany | [111,113,191] |
| Dreb/Deeb | Germany | [65,66] |
| Drehkrankheit ^a | Germany | [82] |
| Gaubber/G(n)aup(p)er ^b | Germany | [29,66,110,111,113,191] |
| Gnubberkrankheit ^c /Gnub(b)ern | Germany | [32,111,126,182,183,205] |
| Goggles | England | [13,34,39,120,128,186] |
| Knopper/Knubber(n)/(K)nupper | Germany | [65,111,113,161] |
| Khujali | Tons (India) | [101,207] |
| Kreu(t)zdrehe(n) ^a | Germany | [11,65,66,191,192] |
| Kreutzschlagen | Germany | [7,113] |
| La maladie convulsive | France | [120] |
| La maladie foll(i)e | France | [21,24,87,120] |
| La maladie trotteurs | France | [24] |
| La prurigo lombar | France | [21,120] |
| La Tremblante | France | [21,24,70,87,128,135] |
| Mukoo | Gangotri (India) | [101,207] |
| Petermännchen | Germany | [57] |
| Prurigo lombar | France | [24] |
| Prurigo lumbar | Spain | [202] |
| Reiberkrankheit | Germany | [21,126,189,191] |
| Reiber-Uebel | Germany | [29,191] |
| Rickets | England | [21,40,196] |
| Rida | Iceland | [50,133,170] |
| Rub/Rubbers | England | [21,90,120,173,203] |
| Rubbing disease | England | [136] |
| Ruppe | Germany | [66] |
| Scabies dorsalis | Germany | [191] |
| Schrucken/Schru(c)kigsein | Germany | [66,126,143,161,182,191] |
| Scratchie | Scotland | [120] |
| Shakings | England | [21,120,128] |
| Shrewcroft | England | [120,128] |
| Shrugginess | England | [136] |
| Spruckigkeit | Germany | [111,113] |
| Tempermänner | Germany | [57] |
| Trab(en)/Traberkrankheit | Germany | [21,87,118,135,161,205] |
| Trotting disease | England | [50,132,136] |
| Trzęsawka | Poland | [120] |
| Wetzkrankheit | Germany | [126,143] |
| Yeukie pine | Scotland | [87] |
| Zitterkrankheit | Germany | [21,120,126] |

^a Many authors consider this nomenclature to be a misnomer based on a mistake [57,66,88,111,126,153,161,171,180,191].

^b This disease, too, was presumed to be different from scrapie [110].

^c Wagenfeld [192] considers Gnubberkrankheit to be different from ‘Kreuzdrehe’ and ‘Traberkrankheit’.

Whichever trait sheep were selected, it is reasonable to consider resistance against scrapie not to be one of these qualities at that time. In fact, it is conceivable that breeding for good wool quality involved inadvertent breeding for susceptibility for scrapie. However, as detailed records of the animals used for breeding during the middle ages are hard and information about their genotype is impossible to come by, this is an eventuality that is impractical to prove or disprove in hindsight.

Today, there are additional reasons for genetic selection. One of them is conservation of species and their gene pool. E.g., the Rhönschaf¹¹ was supposed to be close to extinction during the second half of the 20th century. In 1957, only 300 Rhön sheep were known in West-Germany [89](down from 13,855 in 1948 [22,166]). This reduction was mostly due to a general reduction in the number of sheep, and partly due to the exclusion of Rhön sheep living in Thuringia from breeding on account of the border separating East- and West-Germany until 1989 (300 ewes were reported to live in the former German Democratic Republic in 1990 [166]).

¹¹ <http://www.aid.de/landwirtschaft/tierspecial/schafressen/rhoenschm.htm>.

Table 2
Polymorphisms in the prion protein sequence in sheep.

| Codon | Amino acids | |
|-------|-------------|-----------------|
| 136 | A ↔ V | Ala ↔ Val |
| 154 | H ↔ R | His ↔ Arg |
| 171 | H ↔ Q ↔ R | His ↔ Gln ↔ Arg |

According to Refs. [96,185,200].

Efforts were undertaken to increase the size of the remaining herds. Today, the Rhönschaf is ubiquitous again in the Rhön with about 3000 ewes [89]. A second reason for today's genetic selection is the utilization of knowledge about the genetic layout of individuals, which can be used to select for resistance or against susceptibility to specific diseases.

Only recently, Commission Regulation 999/2001 [58], 1492/2004 [59] and 1428/2007 [60] of the European Community were released aimed at eradicating TSEs. The last two of these regulations proposed the preference of animals carrying the genotype A₁₃₆R₁₅₄R₁₇₁ (or ARR, for short) for breeding. There are 12 different combinations of codons at position 136, 154 and 171 in ovine PrP (Table 2), none of which are pathogenic. Instead, some of these polymorphisms raise the susceptibility for scrapie, while others lower it, a conception that was already formulated in 1826 [182], self-evidently without any knowledge about the molecular genetic fundamentals. One of these polymorphisms (ARR) is considered to provide sheep with the lowest susceptibility to scrapie.

Clearly, this technique was only available after the sequence of PrP was discovered and epidemiological studies could correlate the genotype of sheep with the susceptibility for scrapie.

4. Transmission experiments

Most publications contain statements for or against the discussed modes of transmission. Many authors were convinced that scrapie was transmitted by sexual intercourse [1,2,11,13,32,40,55,56,66,67,88,126,151,152,154,155,160,162,163,171,174,181,188,190,191,206]. However, this opinion was not shared by others [110,161,173,182,183]. Even infection without sexual contact was considered possible [1,118,119,127,129,150,151,155,173] or impossible [13,48,55,66,111,113,126,148,154,171,174,175,181–183,206]. There was another group of authors who favoured the idea of a spontaneous origin of scrapie [57,111,113,154,164,171,182,183,188], one that was refuted by others [127]. Proponents of one cause did not necessarily reject other causes. Some authors changed their mind in the course of time. Thaeer, for instance, was a proponent of sexual transmission in 1821 [181], but turned down this idea in 1826 and suggested a spontaneous origin [182,183]. Other authors considered multiple ways of origin and transmission possible (see Fig. 3).

Most authors reported the main season for contraction to be autumn and the prevalent age of the sheep to be one to three years [111,113,128]. Single authors mentioned lambs and yearlings as vulnerable [155].

M'Fadyean [127] succeeded in demonstrating that lambs housed together with infected ewes for only a few days contracted scrapie 29 months later. However, the diseased sheep were lambs of the infected ewes. Thus, these experiments were unable to differentiate between hereditary and infectious transmission. This complication was acknowledged and advocated against by Gaiger [68] 6 years later, in 1924.

Experiments by M'Fadyean included subcutaneous and intravenous injection of intestinal contents, water containing skin scrapings, up to 25 cm³ of blood, 3 cm³ annattois and foetal cotyle-

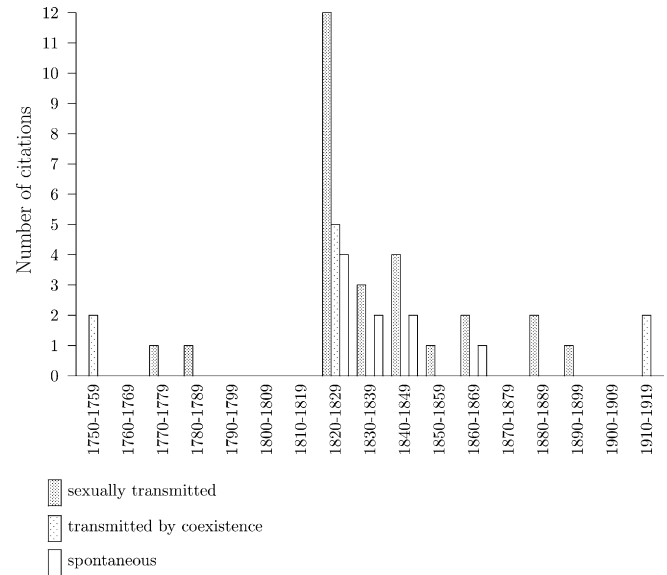


Fig. 3. Number of citations suggesting different ways of transmission.

dons and up to 7 cm³ of cerebrospinal fluid derived from diseased animals [127]. None of these experiments was capable of transmitting scrapie.

The same author also reported an involuntary experiment conducted by two tenants of farms who had almost exactly the same story to tell [127]. Both of them had scrapie-free flocks of sheep. Both of them bought ewe lambs in the autumn of 1907 from the same breeder. In the spring of 1909, the first cases of scrapie appeared in the flocks, exclusively affecting the animals bought in 1907. All these animals bought in 1907, including their offspring, were sold in autumn 1909, whereupon the farms were scrapie-free for one and a half-year. In spring 1911, the disease reappeared, this time affecting animals that had been bred on the farms before the purchase in 1907, thus demonstrating that an infectious process must have taken place between the formerly existing animals and the purchased ones. Based on these and other observations, Gaiger [68] suggested sexual intercourse as the most likely mode of transmission.

Only in 1936, Cuillé and Chelle succeeded in demonstrating scrapie's transmissibility beyond any doubt. After an observation period of 1 1/2 years before the inoculations to demonstrate the absence of scrapie, the authors inoculated their experimental animals intraocularly, epidurally, subcutaneously and intracerebrally using suspensions from brain and spinal cord. Many of their experimental animals died after inoculation from unrelated diseases (mostly inflammations). From the surviving animals, both sheep [44–46] and goats [47], as recipients, could be infected. However, while the incubation periods for sheep were between 11 and 22 months, goats stayed apparently healthy for a duration of 25–26 months. The authors found no differences in the presentation of natural and experimentally infected animals [45].

Former experimenters expected comparatively short incubation periods and therefore abandoned their experiments after this period of time if no symptoms were visible. Others used animals originating from flocks (or even descending from ewes) which were infected with scrapie. After being unsuccessful in their attempts to transmit scrapie, the recipient animals were sold to the butcher [127]. Cuillé and Chelle were the first to adhere to two important circumstances *in combination* in their experimental design:

1. they expected an exceptionally long incubation period of years instead of days or weeks as it was observed in other infectious diseases;
2. they used recipient animals that originated from scrapie-free flocks which had been observed for 18 months before the inoculation to confirm their health.

Greig, in 1940 [79] and in 1950 [80], reported an experiment that started in 1932 to demonstrate the natural transmission of scrapie. Two flocks of sheep, one scrapie infected, the other not, were grazed alternating on the same paddock. Care was taken that during exchange of the sheep, which was twice a week, no immediate contact between the members of the two flocks was possible. 39 months later, seven (and possibly three more, which were doubtful) animals of the flock that had been free of scrapie developed scrapie symptoms, thus demonstrating that a transmission of the disease was also possible without artificial inoculation.

In 1946, Gordon [76] described another accidental experiment concerning the infectivity of scrapie. Between 1931 and 1934, trials to test a vaccine against looping-ill were conducted. Sheep were infected with looping-ill virus by intracerebral inoculation. Three batches of 10% saline suspension were made from the brains, spinal cords and spleens of 140, 114 and 44 treated sheep, respectively, sufficient to immunize more than 44,000 sheep against the disease. 0.35% formalin was added to these suspensions to inactivate the looping-ill virus. During 1935 and 1936 the vaccine proved its effectiveness against looping-ill. In autumn 1937, the first cases of scrapie appeared in a group of vaccinated animals where scrapie had not been observed before. By reconstructing the vaccination schedule, batch number two could be identified as the one that must have transmitted this unexpected disease. Several lessons were learned from this accident:

1. scrapie is definitely transmissible (which was still not demonstrated at the time of vaccination as Cuillé and Chelle's [44–47] experiments describing successful transmission were yet to be published);
2. the scrapie agent is found in the brain, the spinal cord and/or the spleen of diseased animals (from which the vaccine was produced);
3. the scrapie agent is resistant to treatment with formalin. Gordon [77] reported values of 10% formalin for at least 28 months that the agent can withstand without inactivation;
4. subcutaneous inoculation is a possible way of transmission;
5. the incubation period is 2 years or longer.

The influence exerted by the inactivated looping-ill virus was analyzed by Stamp et al. [172]. They inoculated twenty sheep intracerebrally with 1 ml scrapie sheep brain pool (SSBP) each, an inoculum developed to standardize experiments with scrapie infection. Half of these sheep were additionally infected with looping-ill virus 4 months later. The brains and spleens of the double infected animals were made to looping-ill vaccine which was treated with 0.3% formaldehyde for 2 weeks at 4 °C. From the brains and spleens of the sheep infected with scrapie only a control inoculum was prepared. The vaccine and the control inoculum were injected subcutaneously into 30 sheep each. Two of the sheep receiving the looping-ill vaccine and five of the sheep receiving the control inoculum contracted scrapie after incubation periods as short as 5 and 8 months, demonstrating that the addition of looping-ill virus did not assist in transmission of scrapie.

While in Gordon's vaccinations, the way of transmission could be reconstructed unambiguously, there are many reports about scrapie infections where the route of infection is equivocal. One conceivable way of infection, which was rejected by some

researchers [32,160], but was suggested once again in 1954 by Sigurdsson [170], is through vectors. While Wisniewski et al. [199] and Carp et al. [31] described mites as vectors, Post et al. [142] were unable to reproduce these results. Instead, they demonstrated transmission of scrapie through fly larvae and pupae.

Clouscard et al. [35] transmitted scrapie to sheep by feeding them third-stage nematode larvae. The authors supposed that the infectivity present in the ground for several years was insufficient to promote disease. However, upon infection with large numbers of larvae introduced into the ovine gastrointestinal tract, lesions created by these larvae facilitated penetration of the agent.

The accident during looping-ill vaccination was not the only iatrogenic transmission of TSEs. From 1974 on, reports started to appear that described transmission of CJD to humans during corneal transplantation [54], with stereotactic electrodes [23], through pituitary gonadotrophins [36,114], through pituitary-derived human growth hormone [63,114], through dura mater grafts [14–17,179] and during liver transplant [42]. Finally, the transmissibility of scrapie through blood transfusion was demonstrated in sheep [93,95,97], raising concerns for human blood recipients.

5. Theories about the nature of the infectious agent

Despite the different propositions for the nature of the infectious agent, it should never be forgotten what Gajdusek and Gibbs [71] had to say about the conception of a 'virus'. They considered it a 'semantic problem' if an 'agent that transmits disease and turns on its own synthesis' should be called a virus or not. Finally, Gajdusek [70] defended his notion of a 'virus' with the comparison to computer viruses which are known not to contain any nucleic acid either, but, nevertheless, are infectious and self-sufficient enough to support their own replication and subsequent propagation using machinery of the host.

In the following table, a timeline summary of the most important theories about the infectious agent, including arguments for and/or against the individual opinions, is presented.

1914: Based on observations made by others, M'Gowan [128] suggested an association between sarcocysts and emaciation. Other symptoms associated with scrapie, such as itching and paralysis were believed not to be observable 'in the riot of a slaughter-house'. Another explanation for the missing absence of record of scrapie specific symptoms was the fact that inspectors in abattoirs most often only saw carcasses which obviously could not demonstrate any suspicious behaviours. The author claimed to have found a correlation between the presence of sarcocysts and scrapie: 'The sarcocyst is always present in the skeletal muscle of scrapie sheep in large numbers; and the more advanced the case the larger is the number of the sarcocyst present'. While this might have been pure coincidence, the author failed to present a causative correlation between sarcocysts and scrapie.

1938: After demonstrating scrapie's transmissibility [44], Cuillé and Chelle [45] set out to estimate the agent's size. Therefore, they homogenized 15 cm of spinal cord of an affected sheep in 50 cm³ of physiological serum. This solution was filtered and inoculated. The recipient sheep fell ill 16 months later, prompting the authors to speculate that the infectious agent was a 'filterable virus'.

1954: Sigurdsson [170] speculated whether rida (a chronic encephalitis of sheep) and scrapie could be identical. Unsuccessful attempts to cultivate bacteria causing rida led the author to suspect viruses to be the culprit. In order to abandon the use of the phrase 'chronic' with its connotation of 'irregular and unpredictable course' to characterize rida, Sigurdsson suggested the

term *slow infection*, in summary giving rise to the notion of a “slow virus” as the causative agent.

1966: Alper et al. [9] irradiated extracts of brains from infected mice with an electron beam and with ultraviolet radiation of 253.7 nm, which was known to be preferably absorbed by nucleic acids. After finding inactivation by ionizing radiation only at unusually high doses and finding virtually no inactivation by ultraviolet light, the authors concluded that if the infectious agent indeed contained nucleic acid, its length had to be in the range of 800 bases (1.5×10^5 Da), due to the exceptionally small target size observed in the irradiation experiments. Instead, they suggested that the infectious agent ‘is likely to be of an unusual nature’. Discussing these experimental results from Alper et al. as well as the fact that no virus had been observed in scrapie, Field [61] speculated that ‘some new class of particle—perhaps a replicating polysaccharide—might be involved in certain slow . . . “virus” infections’. In a follow-up paper, Alper et al. [8] picked up and endorsed Field’s idea, as ‘some polysaccharides may confer template activity’ for replication of the particle.

1967: Pattison and Jones [140] performed extraction and electro-dialysis experiments with the scrapie agent. Their findings led them to conclude ‘that the transmissible agent of scrapie may be, or may be associated with, a small basic protein’.

One of the first to formulate a “protein only” theory of scrapie pathogenesis was the mathematician J. S. Griffith [81]. He presented three ideas to explain the observed modes of transmission, all of which expected the prion protein to be host encoded. The first idea suggested the prion protein to be silenced by an active repressor. As soon as the infectious prion protein invades the cell, it disables its repressor, thereby activating the transcription of its own gene. This idea is invalidated today by the demonstration that the prion protein is almost ubiquitously expressed [37]. The second idea was nearly identical to what today is thought to be the mode of transmission. By introducing a seed of modified prion protein, the native cellular prion protein molecules are prompted to attach to this seed. Eventually, this grown seed is split into two new seeds, thereby giving rise to its exponential propagation. The third idea, which Griffith rejected based on what was known in 1967, referred specifically to the missing immune response. According to this idea, the prion protein would be identical to, and thereby indiscernible from, an antibody directed against itself. Griffith pointed out that this is not what immunologists call an auto-immune response.

1967: Gibbons and Hunter [75] pondered on the pros and cons of the scrapie agent being a virus, a protein, a carbohydrate or a membrane. Based on the inability to isolate or visualize the scrapie agent, and especially based on the results of radiation experiments, the authors considered the virus theory unlikely, but not entirely dismissible. While the authors acknowledged that the results of many inactivation experiments were compatible with the protein hypothesis, they wondered how a protein could exhibit such exceptional resistance against heat and formalin. Furthermore, treatment with proteolytic enzymes was expected by the authors ‘to produce more marked effects than have been observed if the agent were a simple protein’. The carbohydrate hypothesis was discounted based on the scrapie agent’s sensitivity to ‘treatment with phenol and strong urea—reagents widely used in the isolation of polysaccharides’. Finally, based on results of extraction experiments, which were demonstrated to contain infectious activity ‘even after fifty such “extractions”’, the authors suggested cell membranes to be the infectious agent, which also ‘could well account for conflicting observations of the size of the agent’. Hunter et al. [94] presented a model trying to explain the membrane hypothesis by the assumption of a molecule binding to the membrane and thus modifying its structure. This modified struc-

ture was believed to spread throughout the hitherto unaffected membrane fractions, thus explaining the replication of the agent.

1968: Incorporation (of [3 H]thymidine and uridine diphosphate [14 C]glucose (UDPG)) and centrifugation experiments led Adams and Caspary [3] to conclude that there might be ‘a new DNA-polysaccharide complex in scrapie brain’.

1972: Based on the finding that the potato spindle tuber disease is not caused by a virus, but by ‘a replicating RNA with a molecular weight of about 50,000’, Diener [52] suggested that viroids (as he called them) might also be causative for scrapie. He arrived at this conclusion by comparing features of the scrapie agent with those of the potato spindle tuber viroid (PTSV) and finding several similarities: long incubation periods, absence of virus-like particles in electron microscopy, comparable calculated molecular weight based upon irradiation experiments, extraordinary heat resistance and ‘negligible amounts of detectable infectivity . . . in soluble form in tissue homogenates’. Ten years later, Diener et al. [53] compared viroids and prions and found that some of their features were after all dissimilar. While prions are resistant to RNase, PSTV is sensitive to it. On the other hand, ‘proteinase K and trypsin greatly reduce the titer of the [scrapie] agent’, while PSTV proved to be unaffected by proteases.

1978: Alper et al. [10] extended their irradiation experiments to wavelengths between 237 and 280 nm and to electrons and provided for a way to differentiate between results with and without oxygen in order to account for the effects of radiolysis. Based on the finding that the scrapie agent was more readily deactivated in the presence of oxygen, which the authors described to resemble the behaviour of membraneous systems, they concluded ‘that the component essential for replication contains a lipid fraction’.

1979: Following the detection of spiral-formed inclusions resembling those of *Spiroplasma* sp. in the brain of a CJD victim, Bastian [18] posed the question whether ‘*Spiroplasma* and the transmissible agent of CJD [might] be one and the same’. This proposition was underpinned by the propensity of *Spiroplasma* to infect mice, and the impossibility to detect the CJD agent and *Spiroplasma* serologically. Gray et al. [78] reported similar findings in electron microscopical sections.

1979: Discussing the time course and the temporal behaviour of different scrapie strains, Dickinson and Outram [51] coined the term *virino* for the scrapie agent. It was meant to describe ‘(by analogy with neutrinos) their properties: ‘small, immunologically neutral particles with high penetration properties but needing special criteria to detect their presence’.

1982: Based on the resistance of the pathogen, the protein hypothesis was revived by the introduction of the new term “prion”, which was (and is) meant to denote ‘proteinaceous infectious particle’, by Prusiner [146]. This nomenclature was chosen to ‘underscore the requirement of a protein for infection’. However, at this time, it was not sure whether this particle contains nucleic acid or not, a question that was only answered by the preparation of synthetic mammalian prions [116,117]. The author offered two possibilities for the nature of the agent: ‘(i) a small nucleic acid surrounded by a tightly packed protein coat or (ii) a protein devoid of nucleic acid, that is, an infectious protein’. The author admitted that the second alternative ‘is clearly heretical’. While none of these alternatives was preferred by the author, the emphasis on “protein” was meant to exclude many other theories popular up to this time. However, the belief that there must be some *de novo* synthesis of the pathogen was not abandoned. The author offered two different ways of prion replication for the case that the prion was devoid of nucleic acid: 1. ‘activate transcription of host genes coding for prion protein’ or 2. ‘code for their own replication by reverse translation (protein-directed protein synthesis)’. The time for Griffith’s idea [81] (replication by induc-

ing a conformational change of pre-existing protein) to become conceivable was still to come. However, it was admittedly not known at this time that the prion protein is indeed host encoded [131].

1984: Heat inactivation experiments and comparisons with the behaviour of viruses led Rohwer [158,159] to the conclusion that the scrapie agent could be a virus, a conception that was shared by others [123].

1989: While screening two cDNA libraries constructed from brain membrane and cytoskeletal preparations from scrapie-infected hamster brains, Aiken et al. [6] detected that scrapie 'infectivity is associated with the inner membranes or matrix [of mitochondria] or copurifies with mitochondria and mitoplasts'.

1991: To account for the different strains as well as 'the apparent mutability of the agent', Weissmann [193] suggested the infectious agent to 'consist of two components which together form the *holoprion*. One component is PrP^{Sc} (the *apoprion*) which, even when devoid of nucleic acid, can cause transmissible disease . . . ; the other is a nucleic acid (the *coprion*), of which many variants can exist and which . . . determines its strain-specific characteristics'.

6. Conclusion

Scrapie has been documented since the year 1750, initially in the form of retrospective case reports written by shepherds or their employers. For fear of economic harm, shepherds attempted to keep outbreaks of scrapie secret, resulting in the disease being – especially in the 18th and 19th century – largely unknown to veterinarians. In trying to come up with a meaningful theory about scrapie's transmission, early authors formulated ideas which intermingled characteristics of hereditary, sexually transmissible and infectious diseases. After the demonstration of scrapie to be a transmissible disease in 1936, it took 70 more years until the infectious agent – the prion – could be identified [116,117].

Insufficient importance was given to finding out whether scrapie was curable. Many authors argued against a curability, others claimed to have cured animals [29,113,129,152,155,163,188,190]. A multitude of tested, suggested or rejected cures were described: flushing the patients with cold water [67,171,205], application of sulphuric acid [152,205], injections of lead salt solutions [160] or turpentine oil [88,183], feeding or rubbing the animals with herbal extracts [181,205], application of mercury ointments [88], and burning their spines with red-hot irons [29,64,66,171,181,205,206]. A faster way to get rid of the problem was suggested by several authors, who advised shepherds to slaughter the affected animals and use them for human consumption as soon as they notice this ailment in their herds [1,29,57,88,110,113,118,119,126,128,155,174], since even cured animals were expected to retain damaged genetic material.

While wethers were not considered worthy enough to be cured, attempts to cure breeding animals were discouraged by the prevailing danger of transmission of the disease to the progeny:

A wether wouldn't be worth the effort, but should be culled as soon as the first symptoms are obvious. It is, however, not advisable to cure a breeding animal, because the predisposition for the disease is heritable [181]¹²

If those remedies indeed succeed to cure the patient, I still believe that even cured animals – especially female lambs and

dams –, but also rams that were used as sires in an affected flock, contribute to the disease's further spread [155]¹³

Even now, some 250 years on, a cure for scrapie or any other member of the transmissible spongiform encephalopathies, is not in sight. Now, as then, for scrapie, the only advice that can be given to farmers is to cull all affected animals.

Possibly, in days to come, the current concept of the prion might be ambiguous, too. Prusiner suggested prions to be the pathogenic agents of TSEs in 1982 [146]. Twelve years later, Wickner [195] found similar mechanisms of alternative protein folding to be responsible for traits that were inherited in a non-mendelian fashion in yeast. These prions (in a wider sense) were not associated with disease and widened the concept of the prion. More recently, papers suggest alternative foldings of proteins to be much more common than was expected so far. This might some day open up the door for a revolutionary new concept of long-term memory [49,134,167–169,184], leaving the original concept of the prion – pathogenic agent of TSEs – as a reminiscence of the first important discoveries in prion research.

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¹² Ein Hammel wäre der Mühe nicht werth, sondern ist gleich zu schlachten, wenn die Voranzeigen deutlich genug erscheinen. Ein Zuchthier aber möchte ich nicht curiren, . . . weil . . . die Anlage zur Krankheit sich vererbt [181].

¹³ Denn, wenn die Kur durch jene Mittel in der That selbst gelingen sollte, so würde ich denn doch . . . stets glauben: daß selbst die dergestalt geheilten – zumal Zibbenlämmer oder Mütter – dennoch zur weiter verbreiteten Ansteckung eben so wie diejenigen, ob zwar nur einmal krank gewesen oder auch geheilten, Stähre zugleich beitragen, welche in einer dergestalt durch die Traber-Krankheit einmahl angesteckten Heerde das Fortpflanzungsgeschäft früher selbst zu besorgen gehabt hätten [155].

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