The myth of maternal transmission of spongiform encephalopathy

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It has long been accepted that the pattern of occurrence of scrapie—the form of spongiform encephalopathy associated with sheep—is determined mainly by maternal transmission, and this view has had a profound influence on policy decisions in the control of bovine spongiform encephalopathy and on public concern over the risk to human health from this disease. The occurrence of maternal transmission is, however, not predicted by modern knowledge of the aetiology of spongiform encephalopathy, and even though claims of maternal transmission have been reiterated frequently in the literature, re-examination of the source data reveals that these data are extremely scanty, unreplicated, and probably subject to ascertainment bias. The probability of maternal transmission of spongiform encephalopathy in any species should be viewed with the greatest scepticism.

In assessing the risk to human health of the epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom, the Southwood Committee accepted the view that in scrapie (the spongiform encephalopathy occurring in sheep) “there is transmission of scrapie from the infected ewe to lamb.”¹ Maternal transmission means the infection of the lamb by the dam through a mechanism which is specific to this biological relationship—prenatal or perinatal transplacental transfer of infective agent or infection through milk, saliva, or the close contact of birth and suckling. The House of Commons Agriculture Committee on BSE concluded that if maternal transmission also occurred in bovine spongiform encephalopathy then “its elimination will be much harder and its implications for humans much more uncertain” and “the policy implications would be substantial.”²

In 1989 a long term study was initiated to monitor the possible occurrence of maternal transmission in bovine spongiform encephalopathy.³ Alarm in the general public was fuelled by Professor Lacey, who promulgated the view that for bovine spongiform encephalopathy “vertical transmission should prolong the epidemic into an endemic that would be effectively permanent”⁴ and that if bovine spongiform encephalopathy were to cause spongiform encephalopathy in humans, then not only would many people succumb to this disease, but their children would also be affected.⁵ The issue of maternal transmission in spongiform encephalopathy is therefore very serious and warrants close scrutiny. Transmission of spongiform encephalopathy in humans (kuru and iatrogenic Creutzfeldt-Jakob disease) and animals (bovine spongiform encephalopathy, for example) does occur by specific mechanisms involving food or other contamination, but the extent to which it is involved in the pattern of occurrence of natural scrapie is currently unresolved and is not the subject of this paper.

Many recent publications perpetuate the view that spongiform encephalopathy in sheep (and therefore potentially in other species) is maintained largely

by maternal transmission.⁶⁻⁸ The source papers (see below) on which this claim is based were published in the 1960s, when nothing was known of the molecular genetics of scrapie or the molecular pathogenesis of spongiform encephalopathy and the occasional familial occurrence of the only other endemic spongiform encephalopathy (Creutzfeldt-Jakob disease in humans) was perceived but poorly understood. It is therefore appropriate to consider briefly current understanding of spongiform encephalopathy before reassessing the source data.

Pattern of occurrence of spongiform encephalopathy in species other than sheep

Spongiform encephalopathy can occur as either an epidemic or endemic disease. Epidemics consist of cohorts of cases acquired by contamination with material (usually brain) from affected cases and have occurred in humans as the result of cannibalism in Papua New Guinea (where it is known as kuru⁹) or medical accident^{10,11} or in animals as the result of consuming feedstuff containing protein derived from infected animals. The last has occurred in cattle (bovine spongiform encephalopathy), cats, and exotic ungulates kept in zoos and fed on similar material to the cattle. A similar disease has occurred in farmed mink, captive mule deer, and elk.⁸ There has been no evidence of maternal transmission in any of these epidemics of spongiform encephalopathy.

The incidence of kuru dropped dramatically in people born after the cessation of cannibalism in the mid-1950s, and no children born after 1959 to any of the women who had or subsequently developed kuru have themselves developed the disease.⁹ The preponderance of kuru in women and their children is adequately explained by anthropological data indicating that women and children partook of the brain and other internal organs, and the men did not.⁹

Although there has been a single report of infectivity in placenta, blood, and colostrum from a pregnant woman with Creutzfeldt-Jakob disease,¹² this does not establish maternal transmission since both the child in this case and two further children born to women with Creutzfeldt-Jakob disease¹³ remain well, like the offspring of the kuru patients. Maternal transmission also did not occur from the mice used for transmission by Tamai *et al.*,¹² nor has it occurred in the progeny of a large number of primates used for the study of the transmissibility of human spongiform encephalopathy.¹⁴

Nationwide surveillance of bovine spongiform encephalopathy has shown no greater incidence in the offspring of dams with bovine spongiform encephalopathy than in animals in the same herd whose dam did not have the disease, the incidence in both being consistent with foodborne contamination within these herds.¹⁵ In an isolated cohort of 630 calves, half from dams with and half from dams without bovine spongiform encephalopathy, 40 animals have so far developed

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the disease. But all of these calves came from herds affected by the disease and many were born before 1988 (during the period of exposure to contaminated food) such that until the code is broken (in 1997) these data (supplied by the Ministry of Agriculture, Fisheries, and Food) cannot be used to support the notion of maternal transmission in cattle.

Although it might be thought that the occurrence of bovine spongiform encephalopathy in animals born after the ruminant feed ban of 1988 suggests a non-foodborne mode of transmission, the dramatic drop in the incidence of bovine spongiform encephalopathy in cows born after this date¹⁶ shows that food was the major source of infection. Affected animals born shortly after the ban on the production of this feed have been partly attributable to the "shelf life" of purchased material,¹⁷ and subsequent cases may have been due to inadvertent contamination of cattle feed with banned material. The specified offals ban of 1990, which banned the use of certain bovine offals in all animal feed, was designed to protect other species (in which spongiform encephalopathy had not actually been seen) but would have reinforced the effectiveness of the feed ban for cattle by preventing contamination with potentially infective material. That such contamination was occurring was shown by the geographical association between the density of pig and poultry farming and the incidence of bovine spongiform encephalopathy in cattle born after the ban.¹⁸ An analysis of beef suckler herds which were not fed the contaminated feed but which had "bought in" cases of bovine spongiform encephalopathy provided no evidence of horizontal transmission from animal to animal.¹⁵

Spongiform encephalopathy in a kudu whose dam also had spongiform encephalopathy was initially thought to indicate maternal transmission, but the subsequent appearance of spongiform encephalopathy in several more kudus which were not the progeny of affected animals, as well as in five other species of exotic ungulates born in seven zoos in Britain,¹⁹ suggests that a more widespread source of infection was responsible. All these other exotic ungulates had unaffected dams and were born either before the ruminant feed ban of 1988 or between that ban and the more stringent specified offals ban of 1990. No new cases have occurred since 1992. The animals born between 1988 and 1990 could have been infected by the supposed widespread, but low level, contamination of many types of animal feed, which the specified offals ban seems to have largely eliminated.

The only species apart from sheep (and possibly goats²⁰) in which spongiform encephalopathy is an endemic disease is humans, where the endemic disease is either sporadic or familial. Familial cases occur in an autosomal dominant pattern and are associated with one of a number of point mutations or insertional mutations in the prion gene (PrP gene).²¹ That the mutation causes the disease (rather than conferring susceptibility to an environmental agent) is indicated by the observation that transgenic mice carrying the mouse equivalent of one of these mutations spontaneously develop spongiform encephalopathy.²² The great majority of sporadic cases of human spongiform encephalopathy occur in people who are homozygous for a common polymorphism in the PrP gene.²³

The molecular pathogenesis of spongiform encephalopathy

One of the main conceptual problems in the 1960s, when the notion of maternal transmission was first propounded, was that it was believed that the "genetic" hypothesis of spongiform encephalopathy denied the possibility of the existence of a transmissible agent.²⁴

The undisputed transmissibility of spongiform encephalopathy under experimental conditions was, in that climate, a difficulty for the genetic hypothesis of natural scrapie.

Our current understanding of spongiform encephalopathy is that it can be, under different circumstances, genetic, idiopathic, or acquired in origin²⁵ and that cases of genetic or idiopathic origin give rise to an agent which is then transmissible.²⁶ This is confirmed by transgenic experiments.^{22, 27} In all the spongiform encephalopathies, a normal host protein (PrP^c) undergoes a post-translational modification to an abnormal form (PrP^{sc}). This abnormal form has a high β pleated sheet conformation and spontaneously forms neurotoxic amyloid fibrils, which accumulate in the brain. The primary structure of the PrP protein determines the probability with which it will form an amyloid polymer, so the disease is very rare when the PrP gene is "wild-type" but occurs in an autosomal dominant pattern in cases which carry certain mutations in the PrP gene.²¹ Polymerisation can also be "seeded" by contamination with exogenous PrP^{sc},²⁸ and this accounts for the transmissibility of the disease.

Homozygosity for polymorphisms in the PrP gene enables the protein product of both alleles to interact, making the disease more common in homozygotes.²³ This hypothesis is strengthened by the demonstration of the recruitment of PrP^c by PrP^{sc} in a cell free system.²⁹ That natural sheep scrapie should be a largely recessive genetic disease determined mainly by the primary structure of the host PrP gene, but that tissues from affected cases should transmit disease, both experimentally and occasionally in the field, is wholly compatible with this current view of the spongiform encephalopathies.

The molecular genetics of scrapie

Analysis of the PrP gene in sheep has shown that susceptibility to scrapie is tightly linked to polymorphisms in this gene. There are at least four polymorphic sites (codons 112, 136, 154, and 171), and association between these and the occurrence of scrapie depends largely on the breed of sheep. Susceptible alleles are termed sA and resistant alleles are termed pA, although different combinations of the possible polymorphisms permit the occurrence of alleles of intermediate susceptibility. Sheep with at least one sA allele are susceptible to experimental scrapie after subcutaneous injection of infectious material, and sAsA sheep sometimes show a shorter incubation than sApA sheep, depending on breed—sA is dominant or partially dominant for susceptibility to experimental, peripheral infection.³⁰⁻³²

The pattern of occurrence of natural scrapie is, however, more compatible with a mainly recessive inheritance³³ with only some involvement of heterozygotes.³⁴ In many breeds of sheep, pA alleles are known to encode alanine at codon 136 of the PrP gene and account for more than 85% of the allele frequency in unselected sheep.³⁵ The allele frequency of valine 136 is greater than 95% in sheep with natural scrapie from at least several of these breeds.³⁵⁻³⁷ In cases of natural compared with experimentally induced scrapie, sAsA homozygosity is overrepresented,³⁶ accounting for the largely recessive pattern of the natural disease. In Cheviots, sheep encoding at least one valine at codon 136 show short incubations on subcutaneous challenge with the scrapie isolate SSBP/1,³⁸ whereas sheep homozygous for alanine at codon 136 survive, irrespective of their genotype at codon 171; however, sheep which are homozygous for glutamine at codon 171 show greater susceptibility (than those which carry at least one arginine at codon 171) on experimental infection with another isolate, CH1641, irrespective of

HOLT STUDIOS

Knowing the scrapie status of the rams as well as the dams is vital for interpreting the evidence on transmission of scrapie to lambs

their codon 136 genotype.³⁹ SSBP/1 comprises a pooled sample of scrapie against which sA and pA alleles are defined and has been subject to multiple passage in sA Cheviots. The CH1641 isolate came from a single, natural case of scrapie from a "positive line" Cheviot flock which contained sAsA, sApA, and a few pApA sheep, and was subsequently passaged in pApA Cheviots. Although this occurrence complicates the issue of susceptibility to scrapie, it raises the possibility that this unusual isolate represents the involvement of prion protein from a pA allele and is consistent with the extensive data that different strains of mouse sustain different experimental strains of agent,⁴⁰ even though there is evidence that strain of agent can transcend strain of host.⁴¹ Texel sheep also show a complex pattern of susceptibility, with polymorphisms at codons 136 and 171 both making a contribution,⁴² while in Suffolk sheep susceptibility depends mainly on codon 171 genotype.⁴³

Embryo transfer experiments

Foster *et al.*⁴⁴ reported embryo transfer experiments in which two sAsA and four sApA Cheviot sheep were injected subcutaneously with scrapie agent and about six months later were artificially inseminated with sApA semen. The embryos were transferred to 15 pApA sheep and one sApA sheep. Six of the 20 surviving lambs were sAsA and all these developed scrapie at about 2 years of age. Eleven sApA lambs and three pApA lambs had not developed scrapie at the time of publication. All six donor ewes but no recipient ewes developed scrapie. The most parsimonious explanation of these data is that scrapie in the sAsA animals is genetically determined irrespective of uterine and perinatal environment. To prove this conclusively it will be necessary to look for scrapie in the sAsA progeny of unaffected ewes and rams transferred as embryos into pApA ewes.

The only other relevant embryo transfer experiment is by Foote *et al.*⁴⁵ None of the progeny developed scrapie, but the genotypes of these sheep were not reported, so no firm conclusions can be drawn.

Source data on the maternal transmission of scrapie in sheep

Source material comprises only papers in which authors report their own data for the first time. These fall into two categories: distribution of the agent in tissues, and the familial occurrence of scrapie.

DISTRIBUTION OF AGENT IN TISSUES

Detection of infectivity in tissues requires induction of spongiform encephalopathy in another animal after

injection or feeding of that tissue. Studies in which the recipients have been sheep have been hampered by the fact that if sheep resistant to scrapie are used then transmission is very difficult and if sheep susceptible to scrapie are used then they are likely to develop scrapie naturally.^{46,47} Although scrapie occurred in 19 of 24 sheep susceptible to scrapie that were fed or injected intracerebrally with placental tissue from other sheep affected with scrapie,^{48,49} no data were given of the background level of scrapie in the recipient flock at the time. The incubation period after which the sheep became sick varied widely but, surprisingly, did not depend on the route of administration. Naturally occurring scrapie was subsequently reported in that recipient flock, which had been especially bred for high susceptibility.⁴⁶ Thirty six goats (which were expected to be 95% susceptible to experimental infection) were also used. In the first report,⁴⁸ one of the goats injected intracerebrally and three dosed orally developed spongiform encephalopathy. A further four of the goats dosed orally died of intercurrent disease. The fate of the remaining 24 goats was not mentioned in the subsequent paper.⁴⁹ A sensible interpretation of these reports is not possible given the lack of data and the absence of knowledge of the genotype of the recipient sheep.

When assessed by transmissions to mice, no infectivity was found in semen, ovary, uterus (including fetal contents), fetuses, saliva, milk, colostrum, or mammary gland of sheep affected with scrapie, nor in lambs under the age of 4 months or goats under the age of 11 months.^{50,51} Hourrigan claimed transmission to mice from a small proportion of samples from reproductive organs of affected sheep, but few data were given in this short report.⁵² There is therefore no clear demonstration of the infectivity of the placenta from sheep with scrapie. In reviewing sceptically the lack of evidence for infection of the sheep placenta and its role in natural disease, Hadlow remarked of some people, "For them, it is one of the facts about scrapie."⁵³

Infectivity has been detected in the lymphoreticular system of preclinical, experimentally infected mice,⁵⁴ and it has been proposed that agent is transported from there to the central nervous system by way of the splanchnic nerve and the thoracic spinal cord.⁵⁵ Infectivity has been found in the spleen and in other lymphoreticular and intestinal tissues of Suffolk lambs (which on the basis of their parentage might have been going to develop scrapie) but only those over the age of 4 months.⁵² However, Hadlow has pointed out that "We have no evidence supporting the notion that in the natural infection, virus moves centropetally along nerve fibres from Peyer's patches, mesenteric lymph nodes, or spleen to the the thoracic spinal cord."⁵³ Furthermore, other studies have failed to show consistent levels of infectivity in extraneural sites in some other breeds of sheep,⁵³ and extensive studies in bovine spongiform encephalopathy have failed to detect infectivity in any extraneural tissue of the naturally occurring disease,^{56,57} including placenta (data from the Ministry of Agriculture, Fisheries, and Food), although low levels have been found in the distal ileum of a few experimentally challenged but asymptomatic calves.⁵⁸ Thus the involvement of extraneural mechanisms in the pathogenesis of the disease is unclear. Since the PrP gene is expressed in spleen,⁵⁹ these findings cast little light on the mode of transmission.

FAMILIAL OCCURRENCE OF SCRAPIE

Dickinson *et al.*⁶⁰ compared the incidence of scrapie in the progeny of affected and unaffected sheep taken, in the first generation, from commercial flocks and subsequently mated to form another generation (see table I). The data are, however, inadequately docu-

TABLE I—Progeny of sheep of differing scrapie status affected with scrapie. Values are percentages (numbers)

	Dam×sire	Dam×sire	Dam×sire	Dam×sire
Dickinson <i>et al</i> (1965) ²⁴ Suffolk	High risk×High risk 41 (19/46)	High risk×Low risk 69 (48/69)	Low risk×High risk 10 (4/38)	Low risk×Low risk 18 (5/27)
Dickinson <i>et al</i> (1965) ²⁴ Commercial flocks, Suffolk	Scrapie×Scrapie Not reported	Scrapie×No scrapie 66 (38/57)	No scrapie×Scrapie 12-71 (7-40/56)	No scrapie×No scrapie Not reported
Experimental mating, Suffolk	95 (20/21)	81 (25/31)	Not clear	18 (5/27)
Dickinson <i>et al</i> (1974) ⁴⁰ Suffolk/Blackface F1*	Scrapie×Scrapie 100 (8/8)	Scrapie×No scrapie 62 (20/32)	No scrapie×Scrapie 33 (14/43)	No scrapie×No scrapie 30 (38/125)
Suffolk/Blackface F2*	77 (10/13)	59 (26/42)	45 (10/22)	25 (7/28)
Hourrigan <i>et al</i> (1979) ²⁰ Suffolk	Scrapie×Scrapie 78 (14/18)	Scrapie×No scrapie 42 (13/31)	No scrapie×Scrapie 39 (50/129)	No scrapie×No scrapie 25 (26/105)
Foster and Dickinson (1988) ⁴¹ Suffolk	Scrapie×Scrapie 99 (274/277)	Scrapie×No scrapie Not reported	No scrapie×Scrapie 56 (37/66)	No scrapie×No scrapie Not reported

High risk of developing scrapie was assessed from affected parents; low risk was assessed from unaffected parents.

*F1=progeny of matings of Suffolk×Blackface breeds; F2=progeny of matings of F1.

mented since in commercial practice, as well as in some experimental matings, it is usual for a few rams to tup a large number of ewes, so that the number of lambs reported gives little indication of the number of matings and particularly the number of rams involved. Furthermore, because a few rams are used repeatedly, allele frequencies may vary greatly between groups. Dickinson *et al* suggested that data for the first generation should be ignored because, although the incidence of scrapie in the progeny of affected dams was 66%, the incidence in the offspring of affected sires varied from 12% to 71% per ram. This would be compatible with some of the small number of affected rams being sAsA and others being sApA. Similarly, the occurrence of some affected sApA parents could account for the apparent lack of 100% affliction rate in the progeny in some but not all studies in table I in which both parents were affected.

In the second generation of Dickinson *et al*'s study higher rates of scrapie were found in the progeny of "high risk ewes" mated with "low risk rams" (69%) than of "low risk ewes" mated with "high risk rams" (10%). However, when what seem to be the same high risk rams were mated with high risk ewes the incidence in the offspring was only 41%. Although 75% of high risk ewes in the first group eventually developed scrapie, only 48% of those in the second group did so. Furthermore, only 40% of the high risk rams (two animals) actually developed scrapie. This small number of rams with scrapie makes these data essentially uninterpretable.

Furthermore, Dickinson *et al* reported that it was relatively easy to find lambs with affected dams because they run together in the flock, whereas the sire may have been sold or culled—but in this sort of analysis the status of both parents is equally important. Without rigorous assessment, lambs with affected dams are more likely to have an unknown, affected sire than vice versa. Since the incidence of scrapie where both parents are affected is extremely high any such ascertainment bias would profoundly affect the perceived incidence. It can be seen from table I that the bias towards maternal transmission is much reduced when experimental matings are assessed and is also much reduced in more recent publications. This secular change, along with the current demonstration of the dependence of scrapie on an autosomal gene, makes maternal transmission unsupported by the evidence.

Parry³³ classified his sheep into three risk categories—"black" sheep, which were either affected or had both parents affected; "white" sheep, which came from a scrapie free line and which had already produced many progeny without scrapie; and "grey" sheep, which were of less certain status. The data were drawn from 25 years of stock records of more than 2500 sheep. Thus although the number of sheep reported is still small their choice has been extremely rigorous. Table II shows the proportion of affected offspring in

each type of mating. There is no suggestion of maternal transmission in these data.

Conclusion

Familial patterns of occurrence of spongiform encephalopathy is seen only in the endemic form of the disease, and this occurs only in sheep and humans. With the exception of kuru and iatrogenic Creutzfeldt-Jakob disease (the epidemic forms in humans), spongiform encephalopathy in humans can be regarded as idiopathic, the primary pathogenic event being the spontaneous post-translational modification of prion protein. In sporadic cases, the occurrence of this event is largely confined (with extremely low penetrance) to people who are homozygous for a common polymorphism in the PrP gene; in familial cases, this event is almost inevitable in those with dominant mutations in the PrP gene.

In those breeds of sheep in which it has been assessed, it is clear that natural scrapie is tightly linked to polymorphisms in the PrP gene in patterns which are either recessive or show partial dominance. Thus the familial pattern of scrapie is explicable largely or totally by genetics, and embryo transfer experiments suggest that the perinatal environment is unlikely to be relevant to the pattern of occurrence of natural scrapie.

The debate between the role of genetics and perinatal infection in natural scrapie which took place in the 1960s could not be resolved because the genotype of the sheep could only be partially inferred from the eventual occurrence of scrapie in any particular animal, and transmission studies were hampered by the fact that sheep of unknown susceptibility to natural scrapie were the recipients in transmission experiments. The independent determination of susceptibility to scrapie by sheep genotyping now removes this difficulty and points to natural scrapie being a recessive or partial dominant disease in different breeds of sheep.

Belief in maternal transmission as the main mode of acquisition of natural scrapie has held sway for 30 years on the basis of poorly reported data on the occurrence of scrapie in a handful of sheep of unknown genotype. The genetic basis of spongiform encephalopathy in familial cases in humans, the absence of maternal trans-

TABLE II—Progeny of Suffolk sheep of differing scrapie status affected with scrapie found by Parry.³³ Values are percentages (numbers) of sheep aged 4-5 years

Sire	Dam		
	"Black"	"Grey"	"White"
"Black"	86 (48/56)	46 (57/124)	0 (0/156)
"Grey"	50 (23/46)	17 (18/106)	0 (0/23)
"White"	0 (0/39)	0 (0/7)	0 (0/159)

"Black"=sheep with scrapie or with both parents affected; "grey"=sheep without scrapie but with one first degree relative affected; "white"=sheep without scrapie and no affected relatives.

mission in any other form of spongiform encephalopathy, and the results of embryo transfer experiments all suggest that a genetic basis for natural sheep scrapie is compatible with our current understanding of spongiform encephalopathy. The onus should now be on those who wish to maintain the importance of maternal transmission of spongiform encephalopathy in any species to provide convincing data.

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Commentary: Scrapie revisited

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Scrapie is a naturally occurring disease of sheep, which has become the subject of increased scientific and media interest as scrapie contamination of feed was the probable origin of bovine spongiform encephalopathy. Despite research over the past 30 years, the mechanism of transmission of natural scrapie remains uncertain. The literature on natural and experimental scrapie is extensive and at times confusing, with some authors arguing that scrapie is a purely genetic disorder while others maintain that it is an infectious disease. The advances in molecular biology in recent years have provided new information on scrapie, and Ridley