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Director's Digest

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POSITION PAPER ON BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) FOR THE RENDERING INDUSTRY TO USE FOR REFERENCE AND MEDIA MATERIAL

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INTRODUCTION

BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) IS A NEWLY IDENTIFIED, PROGRESSIVELY FATAL, CENTRAL NERVOUS SYSTEM DISEASE OF BOVINE THAT WAS FIRST REPORTED IN GREAT BRITAIN IN 1986. INCIDENCE OF BSE HAS NOW OCCURRED IN 6,098 DAIRY HERDS AND 799 BEEF SUCKLER HERDS. (WILESMITH, J.W. 1990). THESE FIGURES CONSTITUTE 17.5% OF DAIRY HERDS AND 1.42% OF BEEF SUCKLER HERDS AND IN TOTAL NOT QUITE 10% OF ALL CATTLE HERDS HAVE HAD AT LEAST ONE CASE OF BSE. 60% OF AFFECTED HERDS HAVE HAD ONE CASE, 20% HAVE HAD TWO AND 20% HAVE HAD MORE THAN TWO. (TAYLOR, K. 1990). THERE HAVE NOW BEEN 17,921 CONFIRMED CASES OF BSE. SINCE MARCH OF 1990 THERE HAS BEEN A DOUBLING OF THE INCIDENCE TO 1,200 PER MONTH. THIS IS AN AVERAGE OF 3.6 CASES PER 1,000 ADULT CATTLE. MORE HERDS ARE BECOMING AFFECTED RATHER THAN THERE BEING AN INCREASE IN THE NUMBER OF CASES PER HERD. (WILESMITH, J.W. 1990).

THIS DISEASE HAS ALSO BEEN CONFIRMED IN IRELAND, NORTHERN IRELAND AND IN CATTLE EXPORTED FROM ENGLAND TO OMAN. THERE HAS BEEN NO SCIENTIFIC EVIDENCE TO DATE THAT INDICATES BSE IS A HUMAN HEALTH HAZARD, AND IT IS NOT KNOWN TO EXIST IN THE UNITED STATES. THERE IS NO TEST FOR THE PRESENCE OF THIS DISEASE IN THE LIVE ANIMAL AND THE AGENTS RESPONSIBLE HAVE NOT BEEN COMPLETELY CHARACTERIZED, ALTHOUGH THEIR COMPOSITION APPEARS TO BE VERY SIMILAR WITH A PEPTIDE BEING A MAJOR COMPONENT. THERE ARE THREE CONFLICTING INTERPRETATIONS OF EXISTING KNOWLEDGE, THE AGENT BEING TERMED EITHER A PRION, A VIRINO, OR A FILAMENTOUS VIRUS. MANY U.S. SCIENTISTS BELIEVE IT IS A PRION WHICH IS A SMALL INFECTIOUS PATHOGEN CONTAINING PROTEIN (PRP). IT IS RESISTANT TO PROCEDURES THAT MODIFY OR HYDROLIZE NUCLEIC ACIDS. (SOUTHWOOD, SIR RICHARD, ET AL 1989).

INFECTED CATTLE CAN BE IDENTIFIED ONLY AFTER CLINICAL SIGNS - TYPICALLY APPREHENSIVE AND UNCOORDINATED BEHAVIOR - DEVELOP. THE PRESENCE OF THE DISEASE IS CONFIRMED BY HISTOPATHOLOGICAL EXAMINATION OF BRAIN TISSUE AFTER DEATH. BSE INFECTED BRAIN EXHIBIT CHARACTERISTIC VACUOLES AND ASSOCIATED PROTEIN BUILD-UP CALLED FIBRILS. SCRAPIE ASSOCIATED FIBRILS (SAF) ARE DISEASE-SPECIFIC STRUCTURES, WHICH WHEN DETECTED IN EXTRACTS OF BSE BRAIN, HELPED CONFIRM THAT BSE IS A NEW SCRAPIE-LIKE DISEASE OF CATTLE. THE SAF ARE FORMED FROM AN ESSENTIALLY NORMAL CELL PROTEIN (PRP) WHICH BECOME MODIFIED POSTTRANSLATIONALLY AS A CONSEQUENCE OF INFECTION.

EPIDEMIOLOGY

EPIDEMIOLOGICAL STUDIES IN GREAT BRITAIN INDICATE THAT BSE MOST PROBABLY IS AN EXTENDED SINGLE SOURCE OUTBREAK SPREAD INITIALLY THROUGH CATTLE FEED WHICH CONTAINED RENDERED PROTEIN MATERIAL DERIVED FROM SCRAPIE-INFECTED SHEEP AND LATER BSE CATTLE. THE U.K. IS THOUGHT TO HAVE 15 STRAINS OF SCRAPIE IN THEIR SHEEP POPULATION AND SCIENTISTS IN THE U.K. HAVE POSTULATED THAT A SINGLE STRAIN OF SCRAPIE WAS ALTERED OR EFFECTIVELY EXPOSED CATTLE AT UNUSUALLY HIGH LEVELS, AS A RESULT OF CHANGES IN THEIR RENDERING

PROCESSES (GOING FROM BATCH AND SOLVENT EXTRACTION PROCESSING TO CONTINUOUS RENDERING SYSTEMS) IN THE EARLY 1980'S. THE AGENT THEN BECAME ADAPTED INTO A NEW HOST - CATTLE. WHILE SCRAPIE IS ENDEMIC IN U.S. SHEEP, WE DO NOT KNOW IF OUR SCRAPIE STRAINS PARALLEL THOSE FOUND IN THE U.K. (KING, L. 1990).

A CURRENT UNPUBLISHED STUDY IN THE U.K. (WILESMITH, J.W. ET AL 1990) DOES NOT SUPPORT THE ORIGINAL SUGGESTION THAT THE INTRODUCTION OF CONTINUOUS PROCESSES HAS BEEN THE PRINCIPLE REASON FOR THE EXPOSURE OF CATTLE IN 1981/82 SUFFICIENT TO CAUSE CLINICAL DISEASE AT A DETECTABLE INCIDENCE. THE TIME COURSE OF THE CHANGE TO CONTINUOUS RENDERING IS NOT CONSISTENT WITH THE ESTIMATED TIME OF THE ONSET OF EXPOSURE. CONVERSELY, THE CESSATION OF HYDROCARBON SOLVENT EXTRACTION OF FAT FROM MEAT AND BONE MEAL (MBM) IS CONSISTENT WITH THE TEMPORAL ESTIMATE OF THE ONSET OF EXPOSURE. THIS CHANGE-OVER TOOK PLACE IN THE 1970S AND EARLY 1980S. SOLVENT EXTRACTION HAS BEEN DISCONTINUED EXCEPT FOR A FEW EXCEPTIONS, FOR OVER THIRTY YEARS IN THE UNITED STATES AND AT ITS PEAK UTILIZATION IT NEVER ACCOUNTED FOR MORE THAN TWENTY PER CENT OF U.S. RENDERING PROCESSES.

THE INCUBATION PERIOD IS IN THE RANGE OF 2.5 TO AT LEAST 8 YEARS AND CATTLE RANGING FROM 22 MONTHS OF AGE TO 15 YEARS HAVE BEEN AFFLICTED. (WILESMITH, J.W. 1990). THE CURRENT HYPOTHESIS IS THE EXPOSURE PERIOD LASTED FROM 1981/82 UNTIL AT LEAST 1985 AND IT IS ASSUMED FROM THEN UNTIL 1988 WHEN THE BAN ON FEEDING RUMINANT-DERIVED PROTEIN TO RUMINANTS WAS INTRODUCED. BASED ON STUDIES OF SCRAPIE AND TRANSMISSIBLE MINK ENCEPHALOPATHY (TME), AS WITH MINK, CATTLE COULD BE DEAD-END HOSTS.

THERE IS STRONG EPIDEMIOLOGIC EVIDENCE THAT DIRECT TRANSMISSION FROM COW TO COW DOES NOT OCCUR. SCRAPIE SEEMS TO BE THE ONLY MEMBER OF THE SPONGIFORM ENCEPHALOPATHIES WHERE DISEASE IS DIRECTLY PROPAGATED IN A POPULATION BOTH VERTICALLY AND HORIZONTALLY.

OTHER SPONGIFORM ENCEPHALOPATHIES

SHEEP SCRAPIE - SCRAPIE HAS NOW SPREAD TO 39 STATES IN THE U.S.,

SINCE THE INITIAL DIAGNOSIS IN MICHIGAN IN 1947. INTERESTINGLY, IT HAS BEEN A DISEASE CONFINED MOSTLY TO THE SUFFOLK BREED. OUT OF 478 FLOCKS DIAGNOSED WITH SCRAPIE IN THE U.S., 75% HAVE BEEN SUFFOLK WHERE THE BREED WAS IDENTIFIED. THE RISK OF SPREADING SCRAPIE INTO CATTLE TOGETHER WITH THE INCREASED PREVALENCE OF THE DISEASE IN AMERICAN SHEEP OVER THE LAST TEN YEARS HAS STIMULATED INCREASED FUNDING FOR SCRAPIE RESEARCH AND A NEW EFFORT TO DEVELOP AN EFFECTIVE SCRAPIE CONTROL PROGRAM. CURRENTLY, THERE IS AN ONGOING PROCESS OF NEGOTIATED RULEMAKING IN WHICH REPRESENTATIVES OF PRODUCER GROUPS, MEAT PROCESSORS, RENDERING AND REGULATORY AGENCIES ARE ATTEMPTING TO COME UP WITH A PLAN TO WHICH ALL CAN AGREE. IT IS LIKELY THAT THIS PROCESS WILL RESULT IN A VOLUNTARY CERTIFICATION PROGRAM DIRECTED TOWARD RISK REDUCTION OF AMERICAN SHEEP DEVELOPING SCRAPIE. IN FISCAL YEAR 1990, 38 NEW SCRAPIE-INFECTED FLOCKS WERE IDENTIFIED; INCLUDED IN THIS FIGURE WAS ONE (1) CASE OF SCRAPIE IN A GOAT. THIS IS ONLY THE SECOND REPORT OF SCRAPIE IN A GOAT IN THE UNITED STATES. (DETWILER, L. 1990).

CHRONIC WASTING DISEASES OF MULE DEER AND ELK - FIRST REPORTED BY WILLIAMS AND YOUNG IN 1980 AFTER EXAMING BRAINS OF MULE DEER AND ELK AFFECTED WITH DEBILITATING DISEASES WHILE HELD FOR LONG PERIODS OF TIMES IN ANIMAL PARKS OR ZOOS. MANY SCIENTISTS CONSIDER THIS A NATURAL OCCURRING INFECTION. THE AFFECTED ANIMALS HAD NOT EATEN ANIMAL PROTEINS.

TRANSMISSIBLE MINK ENCEPHALOPATHY (TME) - RARE DISEASE OF RANCH-REARED MINK FIRST RECOGNIZED IN WISCONSIN IN 1947. (HARTSOUGH AND BURGER, 1965). THE DISEASE IS RARE, AFFECTING ONLY 23 MINK RANCHES SINCE THIS TIME. (MARSH, R., 1990). EPIDEMIOLOGIC STUDIES HAVE INDICATED THAT TME IS A FOODBORNE DISEASE HAVING INCUBATION PERIODS OF 7 MONTHS TO OVER A YEAR. (HARTSOUGH AND BURGER, 1965). AFTER THE 1963 INCIDENCE IN HAYWARD, WISCONSIN, TME-AFFECTED MINK BRAIN WAS OBSERVED BY DR. WILLIAM HADLOW TO HAVE HISTOPATHOLOGIC SIMILARITIES TO SCRAPIE. (MARSH, R. 1990).

KURU - A DISEASE OF THE FORE NATIVES IN THE EASTERN HIGHLANDS OF NEW GUINEA. THE INCIDENCE OF KURU HAS DRAMATICALLY DECLINED SINCE THE ELIMINATION OF CANNIBALISTIC PRACTICES. (MARSH, R.F. 1989).

Creutzfeldt-Jakob Disease (CJD) - Affects humans but not geographically limited like Kuru. Classified as a presenile dementia having a prevalence of one per one million population. Approximately 85% of the cases are sporadic with no known source of risk or exposure, while 15% have a familiar pattern of occurrence consistent with autosomul dominant inheritance. Both types are transmissible to subhuman primates. (Marsh, R., 1989). CJD is considered by some scientists as another naturally occurring spongiform encephalopathy. It is as prevalent in vegetarians as meat eaters and in countries without scrapie as those with a high prevalence such as the U.K. (Kimberlin, R. 1990).

Feline Spongiform Encephalopathy (FSE) - Since May of 1990 there have been 10 cats (out of a total of 7 million) diagnosed as dying from SE in the U.K. It is the view of the British Veterinary Association (BVA) that, as the symptoms for FSE are similar to other cat diseases, FSE may not be a new disease in cats. Out of 30 cases referred recently, only two were confirmed as FSE. If the incidence is projected on an annual basis to 21-31 cases per year, then SE in cats could possibly have the same incidence as CJD in humans in Great Britain (McCammont, F. 1990). Another naturally occurring spongiform disease?

AGENT - HOST INTERACTIONS AND PATHOGENESIS

Knowledge of the pathogenesis of these spongiform diseases has been derived largely from studies of scrapie. In natural scrapie, there is early replication and life-time persistence of infection in certain tissues of the lymphoreticular system (LRS), notably Peyer's patches, spleen and lymph nodes. Disease only occurs if infection spreads to the central nervous system (CNS). Studies of experimental scrapie in hamsters and mice indicated the spread of infection along sympathetic nerve fibres which connect with the mid-thoracic spinal cord as part of the splanchnic nerve complex.

The incubation period of scrapie is a precise function of the interactions between the strain of the agent and one major host

GENE; Sip IN SHEEP AND Sinc IN MICE. THESE GENES IMPOSE RESTRICTIONS ON THE MULTIPLICATION OF THE AGENT. IN PARTICULAR, Sinc GENE SEEMS TO RESTRICT THE MULTIPLICATION AND CELL-TO-CELL SPREAD OF SCRAPIE INFECTION AT TWO STAGES OF SCRAPIE PATHOGENESIS. FIRST, AT THE CELLULAR INTERFACE BETWEEN THE LRS AND THE NERVOUS SYSTEM, PROBABLY ACTING ON THE NEURAL SIDE OF THE INTERFACE BECAUSE Sinc GENE EXERTS RELATIVELY LITTLE EFFECT ON SCRAPIE IN THE LRS. SECONDLY, AT THE SUBSEQUENT STAGE WITHIN THE NERVOUS SYSTEM.

THERE IS INCREASING EVIDENCE THAT Sinc AND Sip GENES ARE THE SAME AS THE PrP GENE. INDEED, IT IS LIKELY THAT PrP GENE PLAYS A MAJOR ROLE IN CONTROLLING THE PATHOGENESIS OF ALL MEMBERS OF THE SCRAPIE FAMILY, EVEN THOSE NATURALLY OCCURRING AND EXPERIMENTAL DISEASES IN GOATS, HAMSTERS AND MINK IN WHICH GENETIC EFFECTS HAVE NOT BEEN DESCRIBED; PROBABLY BECAUSE OF THE ABSENCE OF BIOLOGICALLY SIGNIFICANT ALLELIC VARIATIONS AT THE PrP LOCUS IN THESE SPECIES.

THERE IS ALSO EVIDENCE THAT AT LEAST SOME MODIFIED PrP MAY BE AN ESSENTIAL COMPONENT OF THESE INFECTIOUS AGENTS. THE IDEA THAT PrP GENE MAY PROVIDE THE PROTEIN THAT, AFTER POST-TRANSLATIONAL MODIFICATION, PROTECTS THE PUTATIVE NUCLEIC ACID GENOME OF THE AGENT OFFERS AN EXTREMELY SIMPLE BASIS FOR AGENT-HOST INTERACTIONS IN THESE DISEASES.

SIMILAR AGENT AND HOST FACTORS DETERMINE THE "SPECIES BARRIER EFFECT". CHANGING THE HOST CAN CAUSE THE SELECTION OF MUTANT STRAINS OF AGENT WHICH ARE DIFFERENT FROM THOSE IN THE DONOR HOST. IT CAN ALSO CREATE A "DONOR HOST" EFFECT WHICH DOES NOT INVOLVE CHANGES IN THE STRAIN OF AGENT BUT, NEVERTHELESS, CONSTITUTES A BARRIER TO THE INTER-SPECIES TRANSMISSION OF INFECTION, PROBABLY BY REDUCING THE EFFECTIVE DOSE. (KIMBERLIN, R.H. 1990).

RISK ASSESSMENT ON THE POSSIBLE OCCURRENCE OF BSE IN THE UNITED STATES

AFTER CAREFUL EXAMINATION MOST VETERINARIANS AND RENDERERS WOULD

AGREE THAT THERE ARE DIFFERENCES BETWEEN ANIMAL HUSBANDRY PRACTICES AND RENDERING IN THE U.K. VERSUS THE UNITED STATES. THERE WAS NO CLEAR OR SINGLE EXPLANATION WHY IN THE U.K. IN 1982, CATTLE APPARENTLY BECAME EXPOSED TO A TRANSMISSIBLE AGENT SUFFICIENTLY TO RESULT IN A CLINICAL DISEASE. A NUMBER OF FACTORS HAVE BEEN IDENTIFIED WHICH WHEN COMBINED ARE UNDOUBTEDLY SIGNIFICANT IN THE OCCURRENCE OF THIS EPIDEMIOLOGICAL PHENOMENON. (WILESMITH, J.W. ET AL 1988).

THESE INCLUDE: A DRAMATIC INCREASE IN THE SHEEP POPULATION IN GREAT BRITAIN WHICH COMMENCED IN 1980 AND HAS CONTINUED (MAFF 1988); A PROBABLE INCREASE IN THE PREVALENCE OF SCRAPIE INFECTED FLOCKS (WILESMITH, J. W. ET AL 1990); THE GREATER INCLUSION OF SHEEP HEADS IN MATERIAL FOR RENDERING; THE GREATER INCLUSION OF CASUALTY AND CONDEMNED SHEEP IN MATERIAL FOR RENDERING AS A RESULT OF THE REDUCTION IN THE NUMBER OF KNACKERS' YARDS; THE INTRODUCTION OF CONTINUOUS RENDERING PROCESSES DURING THE 1970S AND 1980S WHICH MAY HAVE RESULTED IN THE RENDERING OF ANIMAL MATERIAL AT A LOWER TEMPERATURE AND, OR, A SHORTER TIME THAN PREVIOUSLY AND THE DECLINE IN THE PRACTICE OF USING HYDROCARBON SOLVENTS AND TERMINAL HEAT TREATMENT FOR FAT EXTRACTION SINCE THE MID 1970S. (MMC 1985).

ONE MAJOR DIFFERENCE IN CALF FEEDING PRACTICES IN THE U.K. VERSUS THE U.S. IS THE UTILIZATION OF ANIMAL PROTEINS AS A COMPETING PROTEIN IN U.K. CALF CREEP FEEDS. OVER THE PAST TEN YEARS ONLY SMALL QUANTITIES OF MEAT AND BONE MEAL (MBM) WAS USED IN CALF FEEDS IN U.S. BUT WE ARE NOW BEGINNING TO MOVE MBM IN THIS TYPE OF RATION. IN THE U.K. THEY INCLUDED UP TO 4% MBM IN CALF FEEDS UNTIL RECENT YEARS.

THE U.K. HAS APPROXIIMATELY ELEVEN (11) MILLION CATTLE AND FORTY (40) MILLION SHEEP. THE U.S. SHEEP POPULATION IS ELEVEN (11) MILLION AND WE HAVE 99 MILLION CATTLE PLUS A SUBSTANTIALLY LARGER PORK AND POULTRY INDUSTRY. THE U.K. PROCESSES 1.460 MILLION TONNES OF RAW MATERIAL PER YEAR. ALL E.C. COUNTRIES PROCESS 9.030 MILLION TONNES (KRENK, PER. 1990). THE U.S. PROCESSES 16.363 MILLION TONNES.

The U.K. has a much higher incidence of scrapie than the U.S. and in Southern U.K. where they have the highest incidence of BSE, sheep by-products make up over 15% of the meat and bone meal (MBM). Compare that to less than 1% for all of the U.S. and 1/100 to 1/1000 of one per cent in most U.S. rendering plants. According to Dr. Richard Marsh, conventional rendering inactivates 95-98% of the scrapie agent. Therefore, most U.S. renderers have been inactivating 95-98% of the scrapie agent in the 1/100 to 1/1000 of one percent sheep by-products in their MBM.

Our rendering process may not totally eliminate a scrapie-like agent, but could sufficiently reduce the titre along with our large dilution factor to prevent clinical disease occurring during the normal lifetime of cattle. The incubation period of the scrapie-like infections is related to the dose of agent received, given a constant route of inoculation (Zlotnik, J. and Rennie, J.C. 1967; Lax, A.J., G. C. Millson and E. J. Manning. 1985)

The U.S. is unique in that 85% of the sheep are slaughtered in 15 packing plants and this product is easily identified and can be diverted to other than ruminant diets. For the past ten years some of the sheep by-products from the 15 plants has been cooked separately and sold as a specialty product to non-ruminant animals. The other 15% is slaughtered by hundreds of locker plants throughout the U.S. and this accounts for the small percentage of sheep products in U.S. meat and bone meal before December 1989. With our present program the percentage is even lower.

There was only limited amounts of animal proteins fed to U.S. cattle before 1986. Since that time these products are being primarily fed as a by-pass protein source to lactating dairy cattle. This would indicate that their exposure would be from 2 to 5 years of age on average. Since the incubation period for BSE is estimated to be 3-8 years (Wilesmith et al 1988), it would

SEEM THAT ONLY A SMALL PROPORTION OF U.S. CATTLE WOULD HAVE THE TIME TO DEVELOP BSE BEFORE BEING CULLED FROM THE HERD. (MARSH, R. 1990).

NOT ONLY DID THE U.K. HAVE A MUCH HIGHER LEVEL OF SCRAPIE SHEEP BY-PRODUCTS IN THEIR MBM BUT SOME SMALL RENDERERS IN THE U.K. ONLY PARTIALLY PROCESSED THEIR RAW MATERIAL. THEY USED TO SELL THE PARTIALLY COOKED HIGH MOISTURE GREASY CRACKLINGS TO SOLVENT EXTRACTION PLANTS FOR FURTHER PROCESSING. WHEN THE SOLVENT PLANTS CLOSED IN THE EARLY 1980'S THEY HAD TO MARKET THIS PRODUCT CALLED "GREAVES" TO CONVENTIONAL RENDERING FACILITIES. THERE HAS NOT BEEN OR IS THERE NOW RESTRICTIONS ON THE MARKETING OF GREAVES. (TAYLOR, K. 1990). THERE IS A GEOGRAPHICAL VARIATION IN THE INCIDENCE OF BSE IN THE U.K. AS WELL AS THE REPROCESSING OF GREAVES. (TABLE I). THIS GEOGRAPHICAL VARIATION THEREFORE PROVIDES AN ADDITIONAL EXPLANATION FOR THE GEOGRAPHICAL VARIATION IN INCIDENCE AS MEAT AND BONE MEAL HAS, IN GENERAL, A PAROCHIAL DISTRIBUTION. THE ADDITIONAL HEAT TREATMENT DUE TO REPROCESSING IS LIKELY TO HAVE REDUCED THE-TITRE OF A SCRAPIE-LIKE AGENT IN THE PRODUCT. (WILESMITH, J. W. ET AL. 1990)

IN DECEMBER OF 1989 THE U.S. RENDERING INDUSTRY IMPLEMENTED A SHEEP BY-PRODUCT PROCUREMENT POLICY. THIS RECOMMENDATION SUGGESTS (A) THAT ALL RENDERERS REFRAIN FROM PICKING UP AND PROCESSING DISEASED, DYING, DISABLED AND DEAD SHEEP. (B) RENDERERS AND PACKERS WHO PROCESS SHEEP OFFAL FROM SLAUGHTERING FACILITIES SHOULD DIVERT THE RENDERED SHEEP PROTEIN TO OTHER THAN DAIRY OR BEEF CATTLE FEED. (C) AT SMALL SLAUGHTERING PLANTS (LOCKER) ONLY PICK UP SHEEP OFFAL FROM ANIMALS LESS THAN ONE YEAR OF AGE. DO NOT TAKE ANY SHEEP HEADS. RENDERERS IN DAIRY AREAS OF THE U.S., SUCH AS WISCONSIN AND MINNESOTA, DO NOT RENDER SHEEP OR THEIR PARTS.

IN 1985, A NEW INCIDENCE OF TRANSMISSIBLE MINK ENCEPHALOPATHY (TME) WAS REPORTED ON A MINK RANCH IN STETSONVILLE, WISCONSIN.

(Marsh and Hartsough, 1988). The rancher fed downer cows to the mink and stated he did not feed downer sheep. Much publicity has been given to this incident since two Holstein bull calves were inoculated introcerebrally with mink brain from the Stetsonville ranch. Both animals developed fatal spongiform encephalopathies 18 and 19 months after inoculation (Marsh, R. 1990). In a personal conversation with Wisconsin renderers in November 1990, the Stetsonville rancher stated that he collected animal parts from surrounding slaughtering plants as well as large packing houses. Some of these facilities did slaughter sheep and the rancher did not specify that sheep parts be excluded. He and many other Wisconsin mink ranchers have been feeding downer cows to mink for over thirty (30) years and we have only one possible downer cow/TME relationship.

Since TME has been diagnosed in mink on other mink ranches in Wisconsin where downer cows or other meat products were not fed, could this disease be a naturally occurring spongiform encephalopathy such as chronic wasting disease in mule deer and elk and Creutzfeld-Jakob disease in humans?

Because of the long incubation period associated with spongiform diseases in laboratory animals, they are either inoculated intracerebrally with the test material or fed raw brain. I have not read or heard of scientific studies that demonstrated that animals fed rendered scrapie sheep, TME mink or BSE cattle MBM has caused a spongiform disease in another specie or in the same specie. After one out of ten pigs that received intraperitoneal injections of raw BSE brain tissue became infected with a spongiform disease the U.K. Ministry of Agriculture, Fisheries and Food released the following statement: "Intraperitoneal/intracerebral injections is a highly abnormal route of exposure although it is the most efficient way to measure infectivity". Dr. Richard Kimberlin, a member of the U.K. Tyrrell Committee, pointed out to visiting U.S. renderers that if one (1) unit of infectivity produces the disease

INTROCEREBRALLY, THEN IT TAKES 100,000 UNITS OF INFECTIVITY TO PRODUCE THE DISEASE BY THE ORAL ROUTE. I DO NOT BELIEVE ANYONE KNOWS, AT THIS TIME, THE RELATIONSHIP BETWEEN THE INFECTIVITY OF RAW TISSUE INJECTED INTRACEREBRALLY VERSUS THE INFECTIVITY OF THE SAME TISSUE BEING RENDERED AND FED ORALLY TO CATTLE. (SEE U.K. AND U.S. RENDERING RESEARCH PROJECTS).

USDA AND OTHER U.S. SURVEILLANCE

THE U.S. DEPARTMENT OF AGRICULTURE (USDA) HAS RESPONDED TO THE GREAT BRITAIN SITUATION BY PROHIBITING THE IMPORTATION OF LIVE CATTLE AND ZOO RUMINANTS FROM THE UK SINCE JULY 1989. THERE IS A BAN ON FETAL BOVINE SERUM. PROHIBITIONS AGAINST SHEEP AND GOAT IMPORTATIONS HAVE BEEN IN PLACE FOR MANY YEARS BECAUSE OF THE EXISTENCE OF SCRAPIE IN ENGLAND. THERE HAVE BEEN NO IMPORTATIONS OF BRITISH MEAT OR BONE MEAL FOR A NUMBER OF YEARS BECAUSE OF OTHER RESTRICTIONS AND LACK OF AN ECONOMIC INCENTIVE. IN ADDITION TO ALL THESE IMPORT RESTRICTIONS, THE ANIMAL AND PLANT HEALTH INSPECTION SERVICE (APHIS) HAS STEPPED UP ITS SURVEILLANCE EFFORTS TO VERIFY THAT THE UNITED STATES CONTINUES TO BE FREE OF BSE AND TO BE IN POSITION TO RAPIDLY DETECT THE DISEASE SHOULD IT BE INTRODUCED INTO THE COUNTRY. TRACE BACK AND ACCOUNTING OF CATTLE IMPORTED INTO THE UNITED STATES SINCE 1981 IS ABOUT COMPLETE. BETWEEN 400 TO 500 CATTLE HAVE BEEN IMPORTED FROM THE UK. IN ALL CASES, EITHER THESE ANIMALS HAVE BEEN SLAUGHTERED OR, IF STILL ALIVE, HAVE BEEN INSPECTED. ALTHOUGH NO CNS OR BSE SIGNS HAVE BEEN EXHIBITED, THIS ON-FARM SURVEILLANCE WILL CONTINUE AND IS BEING COORDINATED WITH CANADA.

ARRANGEMENTS ARE NOW IN PLACE TO EXAMINE BRAIN TISSUE FROM CATTLE OVER 2 YEARS OF AGE THAT SHOW SIGNS OF NEUROLOGIC DISEASES. TISSUE SAMPLES FROM THESE ANIMALS WILL BE COLLECTED AT VETERINARY DIAGNOSTIC LABORATORIES IN STATES WITH LARGE DAIRY CATTLE POPULATIONS AND KNOWN SCRAPIE CASES. THERE THEY WILL BE PRESERVED AND SENT IN SPECIAL CONTAINERS TO USDA'S NATIONAL VETERINARY SERVICES LABORATORIES (NVSL) IN AMES, IOWA. APHIS HAS SIGNED A COOPERATIVE AGREEMENT WITH IOWA STATE UNIVERSITY TO CONDUCT MICROSCOPIC

examinations of brain specimens for BSE lesions. Only 30 bovine brains have been submitted to the study to date and all have been negative. APHIS has worked out a protocol whereby any suspicious BSE brains would be referred to NVSL, Ames, Iowa, and reviewed by a panel of expert neuropathologists before a confirmative diagnosis is considered. Since BSE is a foreign animal disease in the United States, confirmation of a first case is a USDA function just like for other foreign animal diseases, e.g., foot-and-mouth disease, hog cholera, or African horse sickness. (King, L. 1990).

Laboratories from the following states first began cooperating in the BSE surveillance program: California, Iowa, Illinois, Indiana, Kentucky, Maryland, Michigan, Minnesota, Missouri, New York, Ohio, Pennsylvania, Tennessee, Virginia, Washington and Wisconsin. Since the organization of the program, additional states have requested to be included, and some 60 diagnostic laboratories are now involved in this network. The Centers for Disease Control (CDC) in Atlanta, Georgia, is also cooperating and is screening brains received from cattle through their public health labs. Most of these samples are harvested from rabies-negative cattle being reviewed by their labs throughout the year.

Over 230 APHIS and State Veterinarians who have special training (now including BSE) in the diagnosis of foreign animal diseases regularly conduct field investigations of suspicious disease conditions throughout the United States. This cadre of experts is part of APHIS's ongoing disease detection network spread across the United States. Any increases in either chronic or acute bovine CNS cases would be picked up by private practitioners or diagnostic labs and reported through these diagnosticians.

APHIS is also working with officials of USDA's Food Safety and Inspection Service (FSIS) to coordinate surveillance for BSE at a number of FSIS-inspected slaughtering establishments that primarily handle mature dairy cattle. APHIS and FSIS officials plan to attend a number of scientific meetings during the rest of the year to discuss the USDA surveillance activity. APHIS

ALSO SERVES AS THE DEPARTMENTAL LIAISON WITH CDC, FOOD AND DRUG ADMINISTRATION, AND THE NATIONAL INSTITUTES OF HEALTH WHICH ALSO HAVE AN INTEREST IN BSE.

AS PART OF THE INCREASED SURVEILLANCE, APHIS IS MOUNTING AN EDUCATIONAL EFFORT TO HELP INFORM U.S. CATTLE PRODUCERS AND VETERINARIANS ABOUT THIS NEW DISEASE. IN ADDITION TO PRESS RELEASES AND FACT SHEETS, A BRITISH VIDEOTAPE ON BSE AND AN INFORMATION PACKET ARE BEING DISTRIBUTED TO ALL APHIS FIELD OFFICES, STATE VETERINARIANS, COLLEGES OF VETERINARY MEDICINE, AND INDUSTRY GROUPS.

RECENTLY A TEAM OF OFFICIALS FROM APHIS, AGRICULTURAL RESEARCH SERVICE (ARS), AND INDUSTRY VISITED GREAT BRITAIN TO SECURE INFORMATION AND GAIN A FIRST-HAND UNDERSTANDING OF THE BSE SITUATION. THE USDA WILL SEND SEVERAL SCIENTIFIC PERSONNEL TO ASSIST IN BOTH AN EPIDEMIOLOGICAL AND RISK ASSESSMENT ANALYSIS. A LABORATORY PATHOLOGIST HAS ALREADY VISITED THE UK TO BECOME FAMILIAR WITH DIAGNOSTIC PROCEDURES. THE RISK ASSESSMENT TEAM WILL COMPARE THE PRODUCTION AND FEEDING PRACTICES IN THE UK AND U.S. RISK FACTORS WILL BE QUANTIFIED, AND ANY ADJUSTMENTS TO THESE PRACTICES THAT WOULD PREVENT OR REDUCE THE PROBABILITY OF BSE OCCURRING IN THE UNITED STATES WILL BE REVIEWED WITH RESPECTIVE INDUSTRIES. (KING, L. 1990).

FOR ALMOST A YEAR, THOUSANDS OF VETERINARIANS, NUTRITION CONSULTANTS, HEALTH OFFICIALS AND DAIRY PRODUCERS HAVE BEEN MONITORING CATTLE FOR SYMPTOMS OF BSE AND NOT ONE CASE HAS BEEN CONFIRMED. TWELVE DAIRY NUTRITION CONSULTANTS, ADVISING DAIRYMEN IN THE UPPER MIDWEST, HAVE THE RESPONSIBILITY FOR MONITORING OVER 100,000 DAIRY CATTLE EVERY 6 WEEKS. THEY REPORT NO EVIDENCE OF BSE IN CATTLE HERDS THAT HAVE BEEN CONSUMING ANIMAL PROTEINS FOR OVER FIVE YEARS.

AS WE EXAMINE ADDITIONAL BRAINS OF ANIMALS THAT HAVE DIED OF DISEASES THAT HAVE SIMILAR SYMPTOMS OF BSE, WE MAY FIND AN ANIMAL WITH SPONGIFORM ENCEPHALOPATHY AND THIS COULD INDICATE THAT MOST SPECIES OF WARM BLOODED ANIMALS HAVE A VERY RARE NATURALLY OCCURRING SPONGIFORM DISEASE. FROM THE INTENSE

SURVEILLANCE CONDUCTED IN THE U.S. FOR THE PAST YEAR WE COULD CONCLUDE THAT IF DR. MARSH IS RIGHT AND THERE IS AN UNRECOGNIZED SCRAPIE-LIKE DISEASE IN U.S. CATTLE THE PREVALENCE IS SO LOW (1 IN 5 - 10,000,000?) THAT THE RENDERED BY-PRODUCTS FROM THESE ANIMALS POSES NO THREAT TO THE HEALTH OF THE U.S. CATTLE POPULATION. THE DILUTION FACTOR WOULD BE SO GREAT THAT IT WOULD BE DIFFICULT TO CALCULATE THE LOW PERCENTAGE IT REPRESENTED OF THE ONE DAY PRODUCTION OF A LARGE RENDERING PLANT. THE SICK ANIMAL MIGHT NOT BE RENDERED AND IF IT WAS, THE MBM MAY NOT BE FED TO CATTLE.

RESEARCH PROJECTS

USDA's ARS HAS ALLOCATED $768,000 FOR SCRAPIE RESEARCH IN FISCAL YEAR 1990. BECAUSE SCRAPIE IS A DISEASE RELATED TO BSE, THIS RESEARCH MAY HAVE IMPLICATIONS FOR BSE. RESEARCH PROTOCOLS WILL BE EXCHANGED WITH GREAT BRITAIN TO AVOID DUPLICATION OF RESEARCH AND TO COORDINATE DATA FINDINGS.

AT THE DECEMBER 1990 MEETING OF THE USDA SCRAPIE/BSE CONSULTANT GROUP, HARLEY MOON, RANDALL CUTLIP, AND JANICE MILLER REPORTED ON-SCRAPIE RESEARCH AT THE NATIONAL ANIMAL DISEASE CENTER (NADA). TO DETERMINE IF CATTLE ARE SUSCEPTIBLE TO THE U.S. SCRAPIE AGENT(S) A TOTAL OF 36 CALVES WILL BE EXPOSED TO INFECTED BRAINS OBTAINED FROM SHEEP IN 5 DIFFERENT FLOCKS. EIGHTEEN CALVES WILL BE EXPOSED ORALLY AND 18 BY INTRACEREBRAL INOCULATION. HALF OF THE ANIMALS WILL BE KILLED AT 1 YEAR AFTER EXPOSURE AND TISSUES ASSAYED FOR INFECTIVITY. THE REMAINDER OF THE ANIMALS WILL BE HELD FOR UP TO 5 YEARS POST EXPOSURE. BOTH NADC AND THE PULLMAN LABORATORY ARE INVOLVED IN A STUDY TO DETERMINE IF THE SCRAPIE AGENT SURVIVES THE RENDERING PROCESS. AT NADC, RENDERED MATERIALS FROM SCRAPIE-INFECTED AND EXPOSED SHEEP ARE BEING FED TO CALVES. HALF OF THESE ANIMALS WILL ALSO BE KILLED AT 1 YEAR AND HALF HELD UP TO 5 YEARS AFTER EXPOSURE.

KATHERINE O'ROURKE AND MARK ROBINSON REPORTED ON RESEARCH IN THE PULLMAN LABORATORY. THE MAJOR EFFORT HERE IS ON DEVELOPING A PRECLINICAL TEST FOR SCRAPIE. SEVERAL APPROACHES ARE BEING TAKEN, INCLUDING THE USE OF IMMUNODEFICIENT (SCID) MICE RECONSTITUTED WITH

SHEEP CELLS TO STUDY EXTRANEURAL REPLICATION OF THE AGENT AND TO CHARACTERIZE AGENT-IMMUNE SYSTEM INTERACTIONS. STUDIES ARE ALSO UNDERWAY TO COMPARE THE BEHAVIOR OF SHEEP SCRAPIE, CATTLE-PASSAGED SHEEP SCRAPIE, AND TRANSMISSIBLE MINK ENCEPHALOPATHY (INCLUDING THE STETSONVILLE ISOLATE) IN CATTLE. IN THE RENDERING STUDY, THE PULLMAN LABORATORY HAS INOCULATED RODENTS WITH BOTH "HIGH-RISK" AND "LOW-RISK" RENDERED MATERIAL. THE HIGH-RISK PRODUCT WAS DERIVED FROM THE RENDERING OF KNOWN-INFECTED SHEEP AND SHEEP FROM SCRAPIED FLOCKS, AND IS THE SAME MATERIAL THAT IS BEING FED TO CALVES AT NADC. THE LOW-RISK MATERIAL WAS PRODUCED BY ADDING 1 INFECTED SHEEP TO A BATCH OF MEAT AND BONE MEAL THAT WAS PRESUMED TO BE UNINFECTED. THE LABORATORY HAS OBTAINED ALL NECESSARY AUTHORIZATION TO CONDUCT BIOLOGICAL ASSAYS OF THE BSE AGENT IN MINK. (PLEASE REVIEW UPDATE OF THIS STUDY ON ATTACHED SHEETS).

IN THE U.K. AN EXPERIMENT HAS BEEN DESIGNED TO EVALUATE THE ABILITY OF CURRENT EC RENDERING PROCESSES, USING PILOT SCALE EQUIPMENT TO DEACTIVATE THE BSE/SCRAPIE AGENT. ADDITIONAL EXTENDED PROCESSING EXPERIMENTS WERE ALSO INCLUDED TO TEST THE RANGE OF BSE/SCRAPIE - DEACTIVATION CONDITIONS.

THE FIRST EXPERIMENT HAS BEEN COMPLETED USING BRAIN TISSUE FROM CATTLE KNOWN TO BE INFECTED WITH BSE. THE FROZEN BRAIN TISSUES WERE MINCED AND MIXED TO PRODUCE A HOMOGENOUS POOL OF INFECTIVE MATERIAL. THE INFECTIVE MATERIAL WAS THEN FURTHER MIXED WITH RAW MATERIAL AND SUBJECTED TO VARIOUS PILOT SCALE RENDERING SYSTEMS.

THE IMPORTANT RENDERING CRITERIA DISCUSSED BY ALL THE PARTICIPATING ORGANIZATIONS DURING THE PLANNING STAGES WERE AS FOLLOWS: RAW MATERIAL CONSTITUENTS; RAW MATERIAL PARTICLE SIZE; RAW MATERIAL MOISTURE/FAT CONTENT; VACUUM/PRESSURE CONDITIONS/ TEMPERATURE/ MOISTURE PROFILE IN CONTINUOUS SYSTEMS; RESIDENCE TIME IN CONTINUOUS SYSTEMS.

DURING THE INDIVIDUAL PROCESSES, VERY EXACTING HYGIENE STANDARDS WERE EMPLOYED TO PREVENT ANY CROSS-CONTAMINATION BETWEEN SAMPLES. THE RESULTING PRODUCTS WERE FIRSTLY TESTED FOR MICROBIOLOGICAL STATUS TO ENSURE PARITY WITH NORMAL PRODUCTION STANDARDS AND THEN PREPARED FOR BIOASSAY AT THE AFRC NPU FACILITY. SAMPLES OF MEAL AND TALLOW WERE SET UP TO BE ASSAYED EITHER QUALITATIVELY OR QUANTITATIVELY AND THE RESULTS FROM THE EXPERIMENTS ARE EXPECTED DURING THE PERIOD MID 1992 - MID 1993. (WOODGATE, S.L. 1990).

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December 10, 1990

Dr. Fred Bisplinghoff
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Dear Fred,

Enclosed is the protocol for testing scrapie-infected rendered products in rodents as we discussed. Since our talk, I have had to modify the number of animals on test because of space limitations. However, I think that the reduced numbers will provide adequate analytical power for our purposes.

Rendering Protocol

Products:

1. high-risk meat and bone meal
2. high-risk tallow
3. low-risk meat and bone meal
4. low-risk tallow
5. high-risk ground animals (not cooked)
6. low-risk ground bones and animals (not cooked)
7. commercial meat and bone meal (from Baker Commodities)

Species on test:

1. outbred golden syrian hamsters
   male (females die young and fight more)
   specific-pathogen-free
   inoculated at approx. 28 days of age
   50ul of 10% suspension intracerebrally or 5 grams of solid by feeding
2. outbred Swiss Webster mice
   female (males kill each other)
   specific-pathogen-free
   inoculated at approx. 28 days
   30ul of 10% suspension intracerebrally or 3 grams of solid by feeding

Test

1. Each of products 1-4 will be inoculated into 40 hamsters and 40 mice by intracerebral injection (320 animals total).

2. Each of products 1-4 will be fed to 40 hamsters and 40 mice as solids (320 animals total).

3. Products 5 and 6 will be inoculated into 20 mice and 20 hamsters by intracerebral injection and fed to the same numbers as solids (80 animals total).

4. Product 7 will be inoculated into 20 mice and 20 hamsters by intracerebral injection (40 animals total).

To date:

High-risk and low-risk meat and bone meal have been inoculated into 32 and 28 hamsters each. More hamsters will be added to this group as they become available. More hamsters are due after the first of the year. A 10% suspension of each product was prepared in a neutral buffer (Tris-buffered saline). It was determined that antibiotics were not necessary in these suspensions, which means that one potentially troublesome variable was eliminated.

Feeding of the meal and tallow to mice will begin this week. The mice I received are too old to do ic inoculations without significant losses. More mice are due next week and after the first of the year.

All test animals in product groups 1-4 should be on-line by the end of January or early February. The rest of the products should be on test by the end of February.

The earliest that we can expect results from hamsters now on test is January. However, it is unlikely that anything will happen in that short of time. If anything is going to happen, I would guess it will be late spring or early summer. If nothing happens to the recipients of product group 5, then it is unlikely that anything will happen with the others. Let's keep our fingers and toes crossed and hope that we end up with a lot of old, fat hamsters and mice.

Sincerly,

Mark

Mark M. Robinson

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TABLE 1. PERCENTAGE OF MEAT AND BONE MEAL (MBM) PRODUCED IN 1988 AS A RESULT OF REPROCESSING GREAVES, BY REGION

	SOUTHERN ENGLAND	MIDLANDS	NORTHERN	SCOTLAND	TOTAL
Tonnes MBM produced per month	6,615	12,339	6,263	3,588	28,805
Tonnes BMB produced per month as a result of reprocessing greaves	12	1,071	1,597	1,400	4,080
% of MBM produced as a result of reprocessing greaves	0.18	8.6	25.5	39.0	14.2
% of dairy herds with at least one confirmed case of BSE (November 1986-July 1989)	12.6	3.9	2.8	1.8	6.3

(Wilesmith, J. W. et al 1990)