PRION DISEASES

(What Clinicians & Diabetologists Should know)

From the Desk of **Professor Sam.G.P.Moses**

"Slow virus Diseases"
"PRION Diseases"
What clinicians & Diabetologists should know about These group of illness – in the wake of Bovine Spongiform Encephalities BSE & BLE.

1. These group of "Slow Virus Neurological Disorders"– are a group of five neurological conditions identified as – KURU Creuzfeldt Jacab Disease – Multi Focal Progressive Leuco Encephalopathy – and Sub Acute Pan Encephalitis & Rubella Encephalopathy etc.

2. Among these Kuru and Creuzfeldt disease share the features commonly referred as "Bovine Sub Acute Spongiform Encephalities"– In Veterinary language familiarly popularized as "Mad Cow Disease".

3. The exact virus is not isolated – Although it is repeatedly mentioned as Slow Virus Diseases – But they are very much associated with protein – "Prion" Proteins and hence better called as Prion diseases.

4. Prion Diseases in Humans & Animals are associated with accumulationof Brain Abnormal "Protease resistance Protein"– "PrP"

5. "Slow virus Diseases" are characterized by long symptomatic incubation Period – Several months to several years – (even 20yrs) between infective agent and clinical illness.

6. Host reaction and accommodation of virus account for the slow reaction probably.

7. Human "Prion" Disease can be divided into three Archeological Characteristics – Sporadic – Acquired and inherited.

8. “KURU” has been of historical importance as first Human Spongiform Encephalities in papua New Guinea – Through practice of “Endo canabolism – Women in particular and young children eating mortuary feasts” “ To honour the Dead” it is told.

9. “KURU” – canabolism as mode of transmission of virus – Native custom of papua New Guinea – due to ritual canabolism – More in Women++ - Men do not eat the bodies of women – Recent decline of canabolic feasts due to imported civilization.

10. Animal Prion Diseases include “Scrapie” in sheep and goats recognized ever 2000 years ago.

11. The appearance of “Bovine Spongiform Encephalopathy”- “ Mad Cow disease” in U. K. since 1986 – Mostly from cattle feeds contaminated etc.

12. Most of the infection in Bovine Spongiform Encephalopathy – is in the Central Nervous System and Lympho Reticular Tissue attempted transmission via muscle is negative.

13. Whether “kuru like Disease can occur in humans through “Bovine Spongiform Encephalopathy” is not established.

14. In general in medicine the virus disease have a Big Tropism – Like Skin Tropism – Parotid Tropism – Hepatic or Pancreatic or Brain Tropism – Thus we are shut up with “Mumps”- breakdown with “Measles” or

Jaundice with Hepatitis etc. Without Tropism usually the organs are not affected.

15. Pancreatitis in animals in cattle is very rare and un common– in horses woody Pancreatitis can occur.

16. In general viruses are protected from entering the pancreas by an Albumin Barrier (R.S.D Leslie). Hence no possibility of BSE in Pancreas.

17. In general animal meat – Beef is so highly processed that it is highly unlikely that they contain any protein.

18. In U.S. ID 50 exertive summary, greatest source if infection include consumption of cattle Brain and Spinal Card and Bone Cuts etc.

19. Insulin is not prohibited from importation under a Federal Law of Food and Drugs. Animal Insulins can be imported by individuals. That is well allowed even in U.S.A.

20. In general Animal Meat – Beet is so highly processed that it is highly unlikely that they contain any “Proteins” PrP” (Prion Proteins).

21. In general the manufacturing process of Insulin from Animals involves several elaborative steps or purification, sterilization and certification as “ Highly purified” – “Monocomponent” etc. and hence the imagination of “Bovine Spongiform Encephalopathy “ & Via Animal Insulins is far from remote.

22. The largest 254BSE amino acid would be filtered out be the 4th o 14th filter steps in manufacturing 14" filter steps in manufacturing.

23. However the Bovine Insulin manufacturers are not at ease in getting at the decline Bovine Insulin Crystals. The reality is not well explained by Big Pharma.

24. In general Bovine Insulin is an Insulin of mixed advantages and theoretical disadvantages – white porcine & Human Insulins are however in one boat together and are often viewed together for long long periods.

25. Still Bovine Insulin is preferred by some Religious Sectors – although porcine more akin to Human Insulins - & at the moment many Human Insulins available in India are of Enzyme Modified Pork variety, i.e. Porcine Insulin converted as "Humanised Porcine" (although original source is porcine) as some of us have labeled it in India.

26. Bovine Insulin is clinically an Insulin of "Theoretical Disadvantages" - mixed with "Advantages" theoretical Disadvantages – may be 3 Amino Acids differ – More antigenicity and antibodies theoretically – More polymeric (Less monomeric) etc and high purification may be positive but not exactly as "Monocomponent" as in Porcine. The advantages may be less of Weight Gain – less of Hypoglyceamia – Less of Hypo Unawareness – more yielding to the formation and manufactures of real "Ultra Lente" - Bovine UltraLente is true peak less Insulin (White Ultra Lente is double peak etc.

27. Thus Human Insulin people always have a step mother attitude to Animal Insulins- Particularly to Bovine Insulins – But however time alone will abolish these controversies – Especially now " A Re – look into animal Insulins" – have come up as a subject to this newer & newer Insulins era.

BSE Risk Assessment Analysis for the Manufacture of Bovine Insulin

(From the desk of Ms.Jenny Hirst Co- Chairman IDDT)

In their statement of 16th April 1996. The European Medicines Evaluation Agency (EMEA) conclude inter alia that for all active ingredients or reagents used in the manufacturing process, the measures detailed in existing European guidelines guarantee that medicinal products containing bovine tissue are safe. There are no recorded cases of variant creutzfeldt Jacob Disease (vCJD) that have been linked to the use of pharmaceuticals containing bovine derivatives.

In considering the risk assessment of Bovine insulins containing material derived cattle, the following should be taken into consideration:

Selection of Animals

- EU legislation has forbidden the use in medicines of certain UK-sourced bovine tissues since March 1990. Between May 1992 and 1999 pancreases were sourced from European countries in accordance with the requirements of the CPMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via medicinal products which state that the country must:

- Have not reported cases of BSE
- Have compulsory notification and clinical and laboratory verification of suspected cases
- Not import cattle from countries with a high incidence of BSE, or progeny of affected females
- Not use feed containing ruminant protein from countries with BSE

Materials may also have been sourced from countries with a low number or indigenous cases if in that country:

- Carcasses of all infected animals are destroyed
- Progeny of affected females are not used
- The feeding to ruminants of mammalian protein (as per commission Decision 94/381/EC) is banned
- Source animals are born after the feeding ban was imposed and not be from herds with reported BSE

Type of Bovine Tissue Used

- The organ used for extraction the pancreas which, according to the CPMP/CVMP Note for Guidance on minimizing the Risk of Transmitting Animal Spongiform Encephalopathies via Medicinal products (EMEA/410/01), is category III material – that is an organ demonstrated to have low levels of infectivity.

Primary Drug Extraction & Purification

- The extraction and purification step for the active drug from the bovine pancreas used has been demonstrated to achieve a log 10 reductions in a spiked scrapie agent is not a requirement of the CPMP Note for Guidance. This validated process has shown the removal of very high levels of contaminated material from test samples processed under manufacturing conditions in a laboratory environment. Spiking of the primary drug processing plant has not taken place.

Secondary Drug Manufacture

- Manufacture of the finished drug product focuses on the risks of cross contamination from other drugs manufactured in the plant for which

dedicated equipment is not used. Cleaning validation for this equipment (formulation vessels, filter housings, filling needles, etc.) applies the company's in-house criteria, which require product-specific analytical methods, if sufficiently sensitive, or TOC methods.

Conclusion

Bovine insulin complies fully with all current European requirements concerning TSEs.

AKZO NOBEL

Diosynth

TO WHOM IT MAY CONCERN

Diosynth B.V., as manufacturer of

BOVINE INSULIN

hereby confirms that this product is manufactured from pancreas glands of bovine origin. Only starting material collected exclusively from BSE/TSE free countries is used as a source.
Moreover, the manufacturing process has been validated for potential prion removal and/or inactivation and was shown to be sufficiently effective (see enclosed summary report).

DIOSYNTH B.V.

Dr. R. Wijnands
Manager QA/Regulatory Affairs

December 2000

Active Pharmaceutical Ingredients

Diosynth bv
PO Box 20
5340 BH Oss
The Netherlands
tel. + 31 (0)412 661555
Fax + 31 (0)412 662617
662156

Inveresk Research
TRANENT EH33 2NE SCOTLAND
TELEPHONE: +44 (0) 1875 614545

BOVINE INSULIN: VALIDATION OF THE REMOVAL/INACTIVATION OF SCRAPIE FROM THE MANUFACTURING PROCESS OF BOVINE INSULIN

Certificate No. 030233

Test Material: Bovine Insulin

Sponsor: Diosynth
PO Box 20
5340BH Oss
The Netherlands

Project No. 852949

The manufacturing process for bovine insulin was validated for potential prion removal and/or inactivation according to Inveresk Protocol No. 852949. The scrapie agent, ME7, was used as a model for bovine spongiform encephalopathy.

This study has been designed to conform to the guidelines issued by the EC CPMP Biotech Working Party Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (February 1996), "Guidelines for minimising the risk of transmission from animals to man of agents causing spongiform encephalopathies via medicinal products" (May 1992), the Federal Bulletin No. 40 issued by the German Federal Ministry of Health entitled "Guidelines on safety measures in connection with medicinal products containing body materials from cattle, sheep or goats for minimising the risk of transmission of BSE and Scrapie" (February 1994) and the Federal Bulletin No. 67 issued by the German Federal Institute for Medicines and Medicinal Products entitled "Announcement on the Licensing and Registration of Medicines" (March 1996). The reduction factors obtained are presented below:

Stage	Initial Scrapie Challenge (log_{10})	Reduction Factor (log_{10})	Total Reduction Factor (log_{10})
1	8.59	5.53	> 10.82
2	8.37	> 5.29	

APPROVED BY:

STUDY DIRECTOR: C A Shepherd DATE: 9 Jan 98
A Shepherd BSc MPhil

FAX: +44 (0) 1875 614555
E-MAIL: inveresk.research@iri.iri.bcx400.co.uk
INVERESK RESEARCH INTERNATIONAL LIMITED
REGISTERED OFFICE ELPHINSTONE RESEARCH CENTRE TRANENT EH33 2NE
REGISTERED IN SCOTLAND NUMBER 91779