STUDIES ON BOVINE MANNOSIDOSIS

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ABSTRACT

Bovine mannosidosis is an inborn lysosomal disease of Angus cattle, associated with a deficiency of acidic α-mannosidase and a consequent disorder in the lysosomal catabolism of glycoproteins. Affected calves characteristically show signs of neurological derangement and usually die within their first year of life. The enzymic defect causes abnormal storage of water-soluble oligosaccharide units within membrane-bound vacuoles in various cell-types. Vacuolation is particularly severe in neurones of the central nervous system, reticuloendothelial cells of lymph nodes and liver, and exocrine epithelial cells of the pancreas, salivary glands and lacrimal glands. Certain cell-types of mesenchymal origin, including fibroblasts, mesangial cells, smooth muscle fibres, pericytes and capillary endothelial cells are also affected. There is evidence that the process of crinophagy may be important in contributing glycoprotein substrates to the lysosomal system, at least in the exocrine pancreas, while in some tissues vacuoles appear to develop as dilatations of Golgi apparatus or smooth endoplasmic reticulum. The more usual picture however was that of storage within vacuoles consistent with the structure of enlarged secondary lysosomes.

Mannosidosis is inherited as a simple autosomal recessive disease and whereas acidic α-mannosidase activity is almost completely absent from the tissues and body fluids of affected homozygotes, heterozygous individuals possess a partial deficiency of the enzyme. This gene dosage relationship forms the basis of methods for differentiating heterozygotes from normal animals. A test based on plasma α-mannosidase activity has been evaluated on over 5,000 Angus cattle, and the prevalence of heterozygotes was found to be approximately 10%. Although plasma α-mannosidase activity has been shown to vary between cattle of different age and sex, and significant seasonal, between-herd and even between-mob

differences were demonstrated, the test is suitable for routine use in the control of mannosidosis on a herd basis. A more sophisticated test for mannosidosis heterozygotes, based on α-mannosidase activity in lymphocyte extracts has been developed and evaluated, and is a useful adjunct to the plasma test. Preliminary investigation of a further test, based on enzyme activity in granulocyte extracts, has produced encouraging results.

Included in this thesis is an evaluation of an "experiment of nature" in enzyme replacement therapy, in which a chimeric mannosidosis calf had been endowed with a transplant of lymphocytes from a normal co-twin, due to fused placental blood circulations. This lymphocyte transplant reduced the severity of lesions in the liver, lymph nodes, pancreas and lacrimal glands of the chimeric calf but the vacuolation of neurones in its brain was of the same order of severity as that seen in positive control calves with mannosidosis, and the clinical course of the disease had not been significantly altered. It is concluded that enzyme replacement therapy by infusion of leucocyte suspensions is likely to be most effective in inborn lysosomal diseases with minimal neurological involvement.

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During the pilot testing scheme, assistance in the collection of samples from the field was provided by my wife, Joanne. Automated assays for plasma α-mannosidase activity were performed by Mrs. C. A. Tse and latterly by Mr. C. G. Rammell of the Wallaceville Animal Health Reference Laboratory. Dr. Jolly was ultimately responsible for the designation of genotype of animals tested.

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