Immunology of Transmissible Gastroenteritis as Applied to the Protection of Newborn Pigs

by Candace Anne Kindermann*

Development of effective immunity (active or passive) to a disease by artificial means depends on scientific knowledge of the causative agent, pathogenesis of the disease, and natural immune response to the disease.

Transmissible Gastroenteritis is a generalized viral disease of swine which causes high death loss and morbidity in pigs less than two weeks of age. In older swine, the disease is very mild and may go undiagnosed. The causative agent is a moderately pleomorphic helical RNA virus of the family coronaviridae. It has a cryptogram of R/1: 9/*: S/E: V/O, and consists of a nucleocapsid inside a spherical envelope with club shape peplomeres. Only one serotype of T.G.E. virus has been found. The virus has an average diameter of 144nm, is heat inactivated at 56° C for 45 minutes, ether and chloroform labile, stable at pH 3, trypsin and bile resistant, and has the ability to servive passage through the stomach.

Pathogenesis of the disease includes a short incubation time, with clinical signs appearing eighteen hours to three days post exposure. Transmission of the virus occurs by ingestion, nasal, or airbourne means with a resulting infection of the small intestine's columnar epithelial cells, leading to destruction or alteration of the cells and villous atrophy. Destruction of the cells decreases the function of the small intestine and leads to the malabsorptive syndrome responsible for the clinical signs.

Natural infection of mature swine with T.G.E. virus stimulates development of active immunity with recovery from the disease. Effective active immunity develops eight to nine days post infection and lasts for approxiamtely eighteen months. The mechanism of active immunity to the T.G.E. virus is not known. Two possible mechanisms have been suggested. The first involves continuous antibody production by the plasma cells of the intestinal lamina propria, primarily secretory IgA antibodies, in response to antigenic stiumulation of the gut by the virus. The antibodies produced (IgA secretory), are then secreted into the intestinal lumen and remain in close association with the epithelial cells where they neutralize the T.G.E. virus prior to its absorption and infection of the cells. The second hypothesis involves development of a resistant population of intestinal epithelial cells. Serum antibodies are produced in high titer, with natural infection of mature animals, they are not however, involved in the active immunity process as related to protection of the gut.

Protection for nursing pigs against T.G.E. must be acquired passively, since rapid replication of the virus in baby pig intestine once exposure has occurred does not allow enough time for active immunity to develop before death occurs, and "safe immunogenic agents suitable for stimulation of intestinal immunity against T.G.E. in young pigs are not available as yet because so little is known about the local immune response of the intestines in young animals."[23] Passive immunity in young pigs must be obtained by ingestion of antibodies in colostrum, since there is essentially no placental immunoglobulin transfer in swine. The knowledge of protective T.G.E. antibody passage to nursing pigs via immune sow's milk and colostrum was first observed in the 1950's when it was observed that baby pigs born to sows that had been infected with T.G.E. virus three weeks or more prior to farrowing remained free of clinical signs of the disease

*Ms. Kindermann is a third year student in the College of Veterinary Medicine.

even though the virus was present in the herd. It was then shown through clinical studies that "continuous intake of colostrum and milk antibodies are required to neutralize the ingested virus in the intestinal tract before they can penetrate the intestinal epithelial cells."[21] Assays of the colostrum and milk showed secretory IgA antibodies to be the major type of antibodies present. A strong relationship between the level of secretory IgA and the degree of passive immunity provided has now been shown. IgA secretory antibody is responsible for protection of mucosal surfaces of the body including the intestines which it can effectively reach in the young pig by ingestion due to its resistance to proteolytic enzymes of the stomach. Antibodies (IgA) first appear in the colostrum 14 days post infection and have reached a protective level by day 17. An antibody level of 1:8 or higher was found to be necessary to protect nursing pigs from virulent T.G.E. virus.

With knowledge of passive immunity production in newborn pigs suckling immune sows, Doyle, Bay, and Hutchings in 1953 suggested the practice of immunization of pregnant sows to produce effective passive protection of nursing pigs against T.G.E.. Since this first suggestion, much research has been done with methods of immunization of pregnant sows.

Oral vaccination of pregnant sows three weeks prior to farrowing with gut-derived virulent T.G.E. virus produces sufficient secretory IgA antibody in colostrum and milk to effectively protect newborn pigs against T.G.E. by passive immunity for as long as the pigs nurse the immune sow. IgA secretory antibodies responsible for the passive immunity of nursing pigs, are produced locally in the mammary gland (mechanism unknown), and secreted in the colostrum and milk of the sow. One theory of the mechanism of local production of secretory IgA in the mammary gland, is the relocation of T.G.E. viral sensitized immunocytes from the lamina propria of the intestine to the mammary gland possibly via the blood or lymph, cloning of the immunocytes in the mammary gland and local production of secretory IgA antibodies. "Crabbe, et al, proposed that IgA antibody producing cells after receiving antigenic stimulus in the intestinal mucosa, emigrate to extraintestinal sites where secretory IgA antibody is produced."[20] The disadvantage of oral vaccination with virulent T.G.E. virus is that it perpetuates the disease, and may cause new sites of infection of T.G.E. by spread, and/or spread of other viruses as contaminants of the vaccine. These are undesirable side effects of this method, and have helped to push for continued investigation of other methods of vaccination.

Oral vaccination of pregnant sows with attenuated live T.G.E. virus (high cell culture passage) yields good production of serum neutralization antibodies, but produces only slight to moderate passive immunity in nursing pigs and only a slight decrease in mortality and morbidity with oral exposure to virulent T.G.E. virus. The antibodies present in the colostrum and milk of these sows were shown to be primarily of the IgG class. This failure of production of passive immunity may be due to lack of proper antigenic stimulation of the sow's intestine due to attenuation or antigenic change of the virus itself.

I.M. or S.C. injection of a live attenuated T.G.E. virus in pregnant sows three weeks prior to farrowing did not provide protection to nursing pigs against virulent T.G.E. virus, even though it produced high levels of serum neutralization antibodies. Assay of the colostrum showed that the Ig were primarily of the IgG class. The only vaccine available (that I could find) was T.G.E. = vac^R produced by Diamond Labs. It is a modified live virus of tissue culture origin, which is administered I.M. at six weeks before farrowing and again at two weeks before farrowing. Its efficacy is questionable, as it doesn't prevent death and morbidity but merely decreases the severity of the disease to some extent.

Intramammary injection of pregnant sows with high passage T.G.E. virus has provided little protection for nursing pigs, primarily producing IgG antibodies in the colostrum and milk. Inoculation with virulent virus intramammary, has produced better effects, but results are not consistant, protection of nursing pigs is not predictable, and spread of the virulent virus can occur.

Intranasal innoculation of mature swine with attenuated T.G.E. virus (high cell culture passage) protected the adult swine against oral infection with virulent T.G.E. virus. I could not, however, find any information on passive immunity in baby pigs

produced by intranasal inoculation of pregnant sows at the correct time prior to farrowing. I would like to see some research done in this area. I feel a live t-s mutant strain of T.G.E. could be developed for intranasal vaccination of pregnant sows that would replicate at 33° C only and cause an upper respiratory infection rather than a generalized infection. Hopefully, the viral infection of the nasal mucosa would stimulate the plasma cells of the nasal mucosa, in a similar manner to what occurs in the intestine, with a resulting relocation of viral sensitized lymphocytes to the mammary gland, cloning, and local production of secretory IgA antibodies which would pass in the colostrum and milk to the nursing pigs and provide them with passive immunity against the virulent T.G.E. strain. Death losses with this type of vaccine would be essentially nil since there would be minimal intestinal involvement during development of immunity, and the vaccine would provide protection against intestinal damage due to infection with the virulent T.G.E. virus. Along this same line of thought, may be the use of recombination of a t-s mutant and the wild strain of T.G.E. virus to gain a stable hybrid virus with the advantages of both, to be used for vaccine production.

Further research and more scientific knowledge of the mechanisms of the immune system involved with T.G.E. will need to be discovered before an effective means of control of the disease by vaccination can be obtained. I hope that in the near future with effective vaccination methods, we will be able to include T.G.E. in the growing list of diseases that are no longer of clinical and economical importance.

BIBLIOGRAPHY

1. P. Porter, Ph.D., and W. D. Allen, F.I.M.L.T., Classes of Immunoglobulins Related to Immunity in the Pig, J.A.V.M.A., Vol. 160, No. 4, Feb. 15, 1972, pp. 511-518.
2. G. P. Shibley, B.S., Ph.D., et al, Application of an Intramammary Route of Vaccination Against Transmissible Gastroenteritis in Swine, Veterinary Medicine/Small Animal clinician, Jan. 1973, pp. 59-61.
3. J. Svendsen and Paddy Brown, IgA Immunoglobulin Levels in Porcine Sera and Mammary Secretions, Res. Vet. Sci., 1973, 15, pp. 65-69.
4. J. Thorsen and S. Djurickovic, Experimental Immunization of Sows with Inactivated Transmissible Gastroenteritis (TGE) Virus, Canadian J. Comp. Med., Vol. 35, April 1971, pp. 99-102.
5. Thomas B. Tomasi, Jr., and John Bienenstock, Secretory Immunoglobulins, Adv. Immunology, 9, pp. 1-96, 1968.
6. Proceedings of the International Pig Veterinary Society, 1976 Congress, June 22-24, 1976, Ames, Iowa, U.S.A., pp. k1-k15.
7. Howard W. Dunne and Allen D. Lemon, *Diseases of Swine*, 4th ed., Ch. 7, pp. 168-189, 1975.
8. Frank J. Fenner, *Medicial Virology*, 2nd ed., 1976, pp. 418-420.
9. P. Porter, Transfer of Immunoglobulins IgG, IgA and IgM to Lacteal Secretions in the Parturient Sow and Their Absorption by the Neonatal Piglet, Biochimica et Biophysica Acta, 181(1969), pp. 381-392.
10. Antonio Morilla, et al, Immunologic dissimilarities of Gut and Cell Culture Propagated TGE viruses, *U.S. Animal Health Assoc.*, Committee on Transmissible Diseases of Swine, 76th Annual Meeting, Miami Beach, Florida, Nov. 6-10, 1972.
11. Kyu M. Lee, M.D., Ph.D., et al, Transmissible gastroenteritis in Pigs, J.A.V.M.A., April 1954, p. 294.
12. A. J. Koltveit, TGE Vaccine Needed—But Circumspection Too, J.A.V.M.A., Vol. 156, No. 5, March 1, 1970, pp. 529-530.
13. E. O. Haelterman, D.V.M., Ph.D., Lactogenic Immunity to Transmissible Gastroenteritis of Swine, J.A.V.M.A., Vol. 147, No. 12, Dec. 15, 1965, p. 1661.
14. Ram Krishan Paul GUPTA, Ph.D., Serologic Response of Swine Following Infection or Vaccination with Transmissible Gastroenteritis Virus, Dissertation Abstracts International (1971), 32B, No. 3, p. 1915-B.
15. Robert J. Genco, and Martin A. Taubman, Secretory gamma A Antibodies Induced by Local Immunization, Nature vol. 221, Feb. 15, 1969, pp. 679-681.
16. Donald A. Fuller, D.V.M., TGE Vaccine, Veterinary Medicine/Small Animal Clinician, Dec. 1971, pp. 1206-1208.
17. J. Ditchfield, et al, A Viral Gastroenteritis of Ontario Swine 1. Clinical Illness and Recovery of the Virus, Can. J. Comp. Med. Vet. Sci., Vol. 31, Aug. 1967, pp. 193-196.
18. E. V. DeBuysscher and D. T. Berman, Studies on the Secretory Immune Response in the Pig, pp. 1-5.
19. Eddo Caletti, D.V.M., Ph.D., et al, Comparison of Immunologic Properties of a High and Low Cell Culture Passage of Transmissible Gastroenteritis (TGE) Virus From a Single Isolant, Proc. Annual Meeting of the U.S. Livestock Sanitary Assoc. 1969) 72:361-370.
20. E. H. Bohl, et al, Antibody Responses in Serum, Colostrum, and Milk of Swine After Infection or Vaccination with Transmissible Gastroenteritis virus, Infection and Immunity, Sept. 1972, Vol. 6, No. 3, pp. 289-301.
21. J. Benyeda, et al, Immunological Study of Swine Transmissible Gastroenteritis (TGE), Acta Veterinaria Academiae Scientiarum Hungaricae, tomua 24(1-2), pp. 159-162 (1974).
22. W. W. Bay, D.V.M., M.S., Ph.D., et al, Transmissible Gastroenteritis of Swine—A Study of Immunity, J.A.V.M.A., March 1953, pp. 200-202.
23. Abou-Youssef, M. H., D.V.M., Ph.D., et al, Characterization of Protective Antibodies to Transmissible Gastroenteritis Virus in Serum and Milk of Sows Exposed to the Virus, Proc. U.S.A.H.A., 75, 1972, pp. 329-341.
24. M. H. Abou-Youssef, D.V.M., Ph.D., et al, Distribution of Antibodies to Transmissible Gastroenteritis Virus in Serum and Milk of Sows: Isolation and Identification of the Immunoglobulin Classes of Swine Serum and Milk, Am. J. Vet. Res., Vol. 33, No. 5, May 1972, pp. 975-979.
25. M. H. Abou-Youssef, Ph.D., Distribution of Antibodies to Transmissible Gastroenteritis Virus in Serum and Milk of Sows Exposed to the Virus, Dissertation Abstracts International, (1972), 32B, No. 10, p. 6114B.
26. E. H. Bohl, D.V.M., Ph.D., et al, Immunology of Transmissible Gastroenteritis, J.A.V.M.A., 160(4):543-549, Feb. 15, 1972.

27. E. H. Bohl, Antibodies in Sow's Milk: Protection of Newborn Pigs Against TGE, Reprint from Ohio Report, 58(2):50-51, March-April 1973.
28. S. Djurickovic, D.V.M., Ph.D., and J. Thorsen, D.V.M., Ph.D., Experimental Immunization of Sows Against Transmissible Gastroenteritis, The Veterinary Record, July 18th, 1970, pp. 62-64.
29. Jill Curtis and F. J. Bourne, Immunoglobulin Quantitation in Sow Serum, Colostrum, and Milk and the Serum of Young Pigs, Biochim. Biophys. Acta, 236(1971), pp. 319-332.
30. M. J. Corbel, et al, Immunoglobulin Class in Relation to Neutralization of Transmissible Gastroenteritis Virus, The Veterinary Record, June 3rd, 1972, pp. 658-659.

Common Swine Mycoplasmas

by Sally K. Kennedy*, Michele Gill,† and Daniel O. Farrington, D.V.M., Ph.D.‡

Mycoplasmas are the smallest organisms (200-300nm) that are capable of growth in cell free medium. They are different from bacteria in that they have no cell wall but are bounded by a unit membrane. The typical mycoplasma colony on solid growth medium has the appearance of a "fried egg." Most mycoplasmas require sterol for growth. Non-sterol requiring mycoplasmas are placed into the genus *Acholeplasma.*

Three recognized species of mycoplasmas known to be pathogenic for swine are *Mycoplasma hyorhinis,* a cause of polyserositis and polyarthritis in 3-to-10-week old swine; *M. hyosynoviae,* a cause of polyarthritis in swine over 10 weeks of age; and *M. hyopneumoniae* (suipneumoniae), a cause of chronic pneumonia in swine.

Acholeplasma laidlawii, A. granularun, A. axanthum and other unclassified isolates of the genus *Acholeplasma* are known to occur in swine. Their role as possible primary pathogens has not been made clear to date.

Mycoplasma hyorhinis Infection—Pigs weighing 15-60 pounds (3-to-10-weeks old) show a polyarthritis-polyserositis as the principle lesion associated with *Mycoplasma hyorhinis.* This is also found in young adult swine undergoing stress. Besides localizing in preexisting pneumonias, the organism is thought to induce a primary pneumonia in the pig. Cell culture lines are frequently contaminated by *M. hyorhinis.*

*Ms. Kennedy is a third year student in the College of Veterinary Medicine.

†Ms. Gill is a 1977 ISU graduate in Journalism and Mass Communication.

‡Dr. Farrington is a former associate professor at VMRI and is now with Pfizer, Inc.

The organism prefers serosal surfaces including synovial membranes and is maintained in a herd mainly by a chronic infection in the upper respiratory tract of adult swine. Transmission is by direct contact or aerosol droplets. A febrile septicemia followed by a polyserositis occurs when *M. hyorhinis* enters the blood stream. The primary lesion is characterized by serofibrinous exudate on serosal membranes. Secondary lesions include fibrous pleural, pericardial and peritoneal adhesions. An increased volume of clear to turbid synovial fluid with or without large fibrin flakes is also present.

A typical *M. hyorhinis* colony after 4 days incubation is presented in figure 1. "Fried egg" type colony morphology (up to 1mm in diameter) with no evidence of film and spots is usual.

Mycoplasma hyosynoviae Infection—This disease, which occurs in 80-to-200 pound pigs (3-to-6-months old) and in young adult swine, is usually an uncomplicated, non-suppurative arthritis. Chronic infection of tonsillar and pharyngeal mucosa of adult swine is the primary way this organism is maintained in the herd. Although the articular cartilage appears normal, synovial membranes become swollen, hyperemic, and yellowish, with mild villous hypertrophy. The affected joint characteristically shows an increased volume of serofibrinous or serosanguinous synovial fluid.

Agar grown colonies show typical "fried egg" morphology and measure up to 1 mm in diameter (Figure 2). The elevated central area generally appears to be more prominant