Annotations

Rotavirus vaccines—achievements and prospects

In studies in various parts of the world, especially in tropical countries, rotavirus infection has been shown to cause the most severe and fatal diarrhoeal illnesses in the first two years of life, in areas where the faecal/oral contamination is very high, probably in the first nine months or so of life. The balance of antibodies conferring immunity is still uncertain. Certainly, intestinal immunity does seem to be important, as mediated by IgA. Nevertheless, neonates seem to be comparatively immune to serious rotavirus infection, although undoubtedly they do become infected, but numerous studies have shown that infection in this age group is mild or subclinical.^{1–4} Presumably, this is mediated by maternal (transplacental) IgG, although various efforts to associate resistance with IgG antibody concentrations in the mothers has not been successful.⁵ According to the classical experiments in pigs,⁶ maternal antibody ought not to be effective at all; but perhaps human infants do not react like piglets.

Serotypes of human rotavirus

Four serotypes of human rotavirus are well established, and a fifth has recently been proposed. It is also well established that rotaviruses from different species can infect piglets, sometimes causing diarrhoea, sometimes, as with the human serotypes, causing merely seroconversion. Herds of pigs and flocks of sheep are scanty in the streets of Birmingham, Bethesda, or Tokyo; but in tropical countries where young animals wander in and out of human dwellings at will, ample opportunity must exist for infection of children by animal viruses and vice versa. A good study to determine whether animal rotaviruses do infect young children or human rotaviruses young animals is badly needed.

Do all the serotypes of human rotaviruses need to be included in a vaccine? Animal experiments have shown that infection of gnotobiotic piglets by one serotype certainly did *not* confer protection against infection by another serotype, although it did confer very good protection on challenge with the homologous serotype.⁷ Zississ *et al* found evidence, however, that a bovine rotavirus vaccine candidate seemed to protect colostrum deprived piglets against infection by human rotavirus strains.⁸ Armed with

this information Vesikari *et al* set up a trial in Finland of a bovine rotavirus vaccine, code name RIT 4237.^{9 10} This was given in a dose of $10^{8.1}$ plaque forming units. It was found to be perfectly safe and had no detectable side effects on serum transaminase activity or white cell blood counts, and seroconversion after one dose was 35% in neonates and about 70% in bottle fed infants aged 4–6 months. This vaccine gave over 80% protection during the first winter against clinical significant diarrhoea lasting more than 24 hours. These results were surprising. When the paper came out we went over it with a fine toothcomb looking for an error; there was no error. The vaccine seemed to be protective against a second winter of diarrhoea viruses in the same group of children, although numbers of cases were small: seven in the placebo group, one in the vaccine group (Delem, personal communication). We wait to find out whether the trials now under way in Peru and shortly to begin in The Gambia will show the same sort of protection in tropical countries where the challenge dose of virus is probably much larger than in the hygienic households of Helsinki. One disadvantage of this vaccine is that the dose of $10^{8.1}$ tissue culture infective doses is very large, and the vaccine must be correspondingly expensive to make. Also, because in tropical countries often the only chance of getting a child to the vaccination centre is once early in his life, the child *must* be immunised against polio and measles as well: will the rotavirus vaccine interfere with the polio or the polio with the rotavirus? Some early results from Israel and elsewhere suggest that polio vaccine may interfere with rotavirus vaccine, but not vice versa; more work is required, however, to establish this point beyond doubt.

Other vaccines

Human rotaviruses have now been established in tissue culture, but so far no vaccine trials that I know of have been mounted using tissue culture isolates of a rotavirus isolated from human diarrhoea. A Japanese group have been endeavouring to make cold adapted strains of rotaviruses—that is, rotaviruses that will grow at low temperatures—in the hope that these will be avirulent.¹¹ The National Institutes of Health, Bethesda group, have developed

a vaccine derived from a rhesus rotavirus.¹² This virus has the same neutralisation serotype as human serotype 3. This, unfortunately, in the dosage originally used (about $10^{6.5}$ infective units) caused quite appreciable and occasionally severe febrile responses in children, though not in adults. It did give a high rate of seroconversion in children. At the lower dose of $10^{4.5}$ infective units, however, it was still effective and without serious side effects. This vaccine is at present on trial in Venezuela. The human rotavirus strain WA, adapted to tissue culture in Bethesda, unfortunately caused rises of transaminase activities in human volunteers. This particular virus strain was found to be contaminated with a simian foamy virus derived from the tissue culture cells used, but it is unlikely that this caused the rises in transaminase activities, and perhaps it may be a characteristic of diarrhoea viruses that they cause a temporary increase in transaminase activities. This point has not been adequately investigated in studies of natural infections.

The results with the calf rotavirus vaccine have been unexpectedly good. All previous experience with many other virus vaccines, however, has shown that the more closely the vaccine virus serologically resembles the pathogen it is hoped to block, the better the results.⁷ On that basis we must expect that the rhesus rotavirus vaccine, or a vaccine based upon a mixture of attenuated isolates of human rotaviruses, will eventually give the best results.

A further possibility is the development of 'tailor made' reassortant viruses, some of whose genes are derived from one parent rotavirus (for example, calf), and some from another virus (for example, human).¹² Such a vaccine virus might combine the ease of culture of the calf virus, so making it comparatively cheap to make, with the immunogenicity of the human parent.

Perhaps no one yet has the ideal rotavirus vaccine; trials are very expensive and take a long time. The World Health Organisation has provided much of the impetus and finance in bringing developments on so quickly—after all, it is only 12 years since the human rotaviruses were first found. It will probably be several years before we can assess fully the prospect for successful mass immunisation. But so far the signs are encouraging.

I thank Dr A Z Kapikian for letting me see a proof copy of his paper on alternative approaches to the development of a rotavirus vaccine in the Nobel Symposium of 1985.

References

- ¹ Bishop RF, Barnes GL, Cipriani E, Lund JS. Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. *N Engl J Med* 1983;**309**:72–6.
- ² Chrystie IL, Totterdell BM, Banatvala JE. Asymptomatic endemic rotavirus infections in the newborn. *Lancet* 1978;*i*:1176–8.
- ³ Mata L, Simhon A, Urrutia JJ, Kronmal RA, Fernandez R, Garcia L. Epidemiology of rotaviruses in a cohort of 45 Guatemalan Mayan Indian children observed from birth to the age of three years. *J Infect Dis* 1983;**148**:452–61.
- ⁴ McLean BS, Holmes IH. Effect of antibodies, trypsin, and trypsin inhibitors on susceptibility of neonates to rotavirus infection. *J Clin Microbiol* 1981;**13**:22–9.
- ⁵ Totterdell BM, Chrystie IL, Banatvala JE. Cordblood and breast-milk antibodies in neonatal rotavirus infection. *Br Med J* 1980;**280**:828–30.
- ⁶ Pensaert M. Concepts and experiments on prevention and control of transmissible gastroenteritis of swine in the light of its pathogenesis. *Bulletin Office International des Epizooties* 1971;**76**:105–17.
- ⁷ Gaul SK, Simpson TF, Woode GN, Fulton RW. Antigenic relationships among some animal rotaviruses, virus neutralisation and cross-protection in piglets. *J Clin Microbiol* 1982;**16**:495–503.
- ⁸ Zissis G, Lambert JP, Marbehan P, *et al.* Protection studies in colostrum-deprived piglets of a bovine rotavirus vaccine candidate using human rotavirus strains for challenge. *J Infect Dis* 1983;**148**:1061–8.
- ⁹ Vesikari TE, Isolauri E, Andre FE, *et al.* Protection of infants against human rotavirus diarrhea by the RIT 4237 live attenuated bovine rotavirus vaccine. In: Lerner RA, Chanock RM, Brown F, eds. *Vaccines 85: molecular and chemical basis of resistance to parasitic, bacterial and viral disease*. New York: Cold Spring Harbor. 1984:369–72.
- ¹⁰ Vesikari T, Isolauri E, d'Hondt E, Delem A, Andre FE, Zissis G. Protection of infants against human rotavirus diarrhea by the RIT 4237 live attenuated bovine rotavirus vaccine. *Lancet* 1984;*i*:977–81.
- ¹¹ Matsuno S. Cold adaptation of a human rotavirus strain. In: *Abstract in Working Conference on rabies, arboviruses, including dengue and viral gastroenteritis of Japan-US Cooperative Medical Science Program*. Tokyo: National Institutes of Health, 1984:12.
- ¹² Kapikian AZ, Hoshino Y, Flores J, *et al.* Alternative approaches to the development of a rotavirus vaccine. In: Holmgren J, ed. *Nobel Conference on Recent advances in vaccines and drugs against diarrhoeal diseases*. Stockholm, 1985. (In press.)

T H FLEWETT
Regional Virus Laboratory,
East Birmingham Hospital,
Birmingham B9 5ST