Few studies have focused on the risk to the fetus from passive smoke. One study found that perinatal mortality was higher in the children of fathers who were heavy smokers than in the children of non-smoking fathers.[21] In a study of the relation between passive smoking and birth-weight[10] passive smoking was defined as exposure to another person's cigarette smoke for at least 2 h each day during pregnancy either in the home or at work. About a quarter (23·6%) of the women in the study had not smoked during pregnancy but were exposed to passive smoke. Among these, exposure was significantly related to having a low-birth-weight baby (<2500 g). The relation was seen only in full-term (≥37 weeks) babies. The relative risk of having a low-birth-weight child for exposed women compared with unexposed women was 2·17 (95%, confidence limits = 1·05, 4·50) after adjustment for confounding factors. Babies delivered to mothers exposed to passive smoke were an average of 24 g lighter than those delivered to unexposed mothers.

Since the only information on smoking and drinking in other household members came from the mothers' reports, we considered the possibility that our findings were distorted by biased reporting. For example, smoking mothers might have had a tendency to exaggerate their reports of tobacco use by other family members. In this case, low birth-weight due to maternal smoking would appear to be the result of tobacco use by other family members. We do not believe that such a distortion is present in our data since the effect is not seen in relation to alcohol use.

Mothers might also under-report their own tobacco use but report fully that of other family members. In this case under-reporting of alcohol consumption would also be expected; yet a large proportion (70%) of the mothers in our study reported alcohol consumption during pregnancy. Another study of pregnant Danish women reported a similarly high percentage (77%) of drinkers.[22] That the women in our study generally gave accurate reports of tobacco use also is suggested by the close agreement of our findings with those of other studies.[2,15]

Although we were able, with our model, to explain only 14% of the variance in birth-weight, our findings are not very different from the 17% variance found by Dougherty and Jones.[15] They used similar variables in their model but did not include father's or household smoking. The differences in the models may also be partly due to the omission of maternal and paternal height in our model.

We examined paternal smoking as both a continuous and a discrete variable. Both showed a significant effect of paternal smoking on birth-weight while controlling for the effect of maternal smoking. Although the paternal effect was less than the maternal effect these results suggest that, in addition to direct exposure to smoke from the mother, indirect or passive exposure to smoke from the father may result in an independent effect on birth-weight.

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PROTECTIVE EFFECT OF NATURALLY ACQUIRED HOMOTYPIC AND HETEROTYPIC ROTAVIRUS ANTIBODIES

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Summary To assess serotype specificity of immune resistance to rotavirus gastroenteritis, the relation between pre-existing neutralising antibodies to homotypic and heterotypic rotaviruses and protection against infection or clinical illness was investigated. The subjects were 44 orphans exposed once or twice to consecutive outbreaks of gastroenteritis due to type 3 rotavirus in an orphanage in Sapporo. Sera were collected throughout these outbreaks and the serum levels of neutralising antibodies against four different serotypes of group A human rotavirus were measured before and after the outbreaks. Protection against rotavirus gastroenteritis seemed to be serotype specific and to be related to levels of antibody against homotypic virus. A neutralising antibody level of 1/128 or greater seemed to be protective. The protective effect was of short duration, which was probably the explanation for recurrent attacks of gastroenteritis due to

D. H. RUBIN AND OTHERS: REFERENCES

1. Johnston C. Cigarette smoking and the outcome of human pregnancies: a status report on the consequences. *Clin Toxicol* 1981; **18:** 189–209.
2. Holsclaw DS, Topham AL. The effects of smoking on fetal, neonatal and childhood development. *Pediatr Ann* 1978; **7:** 105–36.
3. Cole H. Studying reproductive risks, smoking. *JAMA* 1986; **255:** 22–23.
4. Gortmaker SL, Klein-Walker D, Jacobs FH, Ruch-Ross H Parental smoking and the risk of childhood asthma. *Am J Public Health* 1982; **72:** 574–79.
5. Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985; **75:** 859–68.
6. Weiss ST, Tager IB, Speizer FE, Rosner B. Persistent wheeze. *Am Rev Resp Dis* 1980; **122:** 697–707.
7. Pedreira FA, Guandolo VL, Feroli EJ, Mella GW, Weiss IP. Involuntary smoking and incidence of respiratory illness during the first year of life. *Pediatrics* 1985; **75:** 594–97.
8. Fergusson DM, Horwood LJ, Shannon FT, Taylor B. Parental smoking and lower respiratory illness in the first three years of life. *J Epidemiol Comm Health* 1981; **35:** 180–84.
9. Tager IB, Weiss ST, Munoz A, Rosner B, Speizer FE. Longitudinal study of the effects of maternal smoking on pulmonary function in children. *N Engl J Med* 1983; **309:** 699–703.
10. Martin TR, Bracken MB. Association of low birthweight with passive smoke exposure in pregnancy. *Am J Epidemiol* (in press).
11. Hollingshead AB, Redlich FC. Social class and mental illness. New York: John Wiley, 1958.
12. Hansen EJ. Ungdom og Uddanelse II. Publication no 47, Social for Skningsinstitutter. Kobenharn: Teknisk Forlag, 1971.
13. Kleinbaum DG, Kupper LL. Applied regression analysis and other multivariable methods. Boston: Duxbury Press, 1978.
14. Cohen J, Cohen P. Applied multiple regression/correlation analysis for the behavioral sciences. New Jersey: Lawrence Erlbaum Associates, 1983.
15. Dougherty CRS, Jones AD. The determinants of birthweight. *Am J Obstet Gynecol* 1982; **144:** 190–200.
16. Showstack JA, Budetti PP, Minkler D. Factors associated with birthweight: an exploration of the roles of prenatal care and length of gestation. *Am J Public Health* 1984; **74:** 1003–08.
17. Davies DP, Gray OP, Ellwood PC, Abernethy A. Cigarette smoking in pregnancy: associations with maternal weight gain and fetal growth. *Lancet* 1976; i: 385–87.
18. Greenberg RA, Haley NJ, Etzel RA, Loda FA. Measuring the exposure of infants to tobacco smoke, nicotine and cotinine in urine and saliva. *N Engl J Med* 1984; **310:** 1075–78.
19. Matsukura S, Taminato T, Kitano N, et al. Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers: evidence for passive smoking. *N Engl J Med* 1984; **311:** 828–32.
20. Fielding JE. Smoking: health effects and control *N Engl J Med* 1985; **313:** 491–98 and 555–61.
21. Mau G, Netter P. The effects of paternal cigarette smoking on perinatal mortality and the incidence of malformations. *Dtsch Med Wochenschr* 1974; **99:** 1113–18.
22. Olsen J, Rachootin P, Schibdt AV. Alcohol use conception time and birthweight. *J Epidemiol Comm Health* 1983; **37:** 63–75.

a rotavirus of the same serotype. Seroconversions or concomitant antibody responses to type 1 or 4 rotavirus in most children with type 3 rotavirus infection suggested that immunity to heterotypic virus can be induced by a rotavirus vaccine.

Introduction

ROTAVIRUS vaccines are being developed[1-3] because rotaviruses are a major cause of severe diarrhoea of infants and young children everywhere and diarrhoeal diseases are a leading cause of infant mortality in developing countries.[4] However, several questions must be answered before an effective strategy for immunisation can be developed. Two of the most important questions are how long homotypic immunity remains effective in preventing reinfection and clinical illness, and whether heterotypic cross-protection occurs.

During a longitudinal survey of diarrhoeal diseases in an orphanage, there have been three outbreaks of gastroenteritis due to type 3 rotavirus. We report here on the relation between pre-existing homotypic and heterotypic antibody levels and resistance to infection or clinical illness caused by type 3 rotavirus.

Subjects and Methods

Subjects

Outbreaks of rotavirus gastroenteritis occurred at the Hokkaido Central Infant Home, in February, 1981, March, 1982, and October, 1982. During these outbreaks there were 39–45 healthy orphans aged 1–24 months housed in four rooms according to age. All shared a play room. 19 (46%) out of 41 children had diarrhoea during the first outbreak, 25 (62%) of 39 during the second, and 10 (22%) of 45 during the third. 29 orphans were exposed to both 2nd and 3rd outbreaks; 14 of the 29 orphans had diarrhoea during the 2nd outbreak. Faeces were examined for rotavirus by electron microscopy (EM). Out of 36 specimens collected 23 (64%) were rotavirus positive by EM-6, 8, and 9 in the first, second, and third outbreak, respectively. No other virus or virus-like particles were detected. Three isolates, one from each of the three outbreaks, could be successfully propagated in roller tube cultures of MA104 cells; they were identified as subgroup 2 and serotype 3 rotavirus.

Serum Specimens

Pairs of pre and post outbreak sera were obtained from 32 of the 39 orphans exposed to the second outbreak, and from 29 of the 45 exposed to the third. Thus, 61 paired samples were obtained from 44 orphans (17 of whom were exposed to both outbreaks). All 61 "post" sera were collected one month after an outbreak. 32 "pre" sera were collected by chance a week before the 2nd outbreak. 29 pre sera were collected a month before the 3rd outbreak (as post sera for adenoviral gastroenteritis which occurred in July, 1982). Serum specimens were kept at 20°C until tested.

Serology

The paired pre and post outbreak sera were tested for neutralising antibody titres against the four recognised serotypes of human rotavirus by the use of fluorescent-focus reduction assay.[5] Viruses used as antigens were KU strain (type 1), S2 strain (type 2), MK strain (type 3, the current strain derived from the second outbreak), and Hochi strain (type 4).[6]

Results

Relation between Pre-existing Homotypic Antibody Levels and Protection against Infection or Clinical Illness

24/26 children who were seronegative or who had antibody titres of 1/32 or below acquired the infection or fell ill, whereas few of those with antibody titres of 1/64 or more did so; and all but 1 of the 23 children with antibody titres of 1/128 or greater remained well (table I).

Fig 1 shows the relation between level of herd immunity and scale of outbreak. In the March, 1982, outbreak, when most children had antibody titres of 1/64 or below, many had diarrhoea, whereas in the October, 1982, outbreak, when most children had antibody titres of 1/64 or greater, the illness occurred mainly among the few with low antibody levels.

Protection against Reinfection or Illness after Re-exposure to the Same Serotype (Type 3)

3 of the 19 children who had gastroenteritis during the first outbreak were re-exposed to infection during the second outbreak 13 months later; the other 16 had left the orphanage. All 3 were reinfected, as shown by their antibody response or faecal shedding of virus (table II). In 1 of them (patient 1) the infection was subclinical.

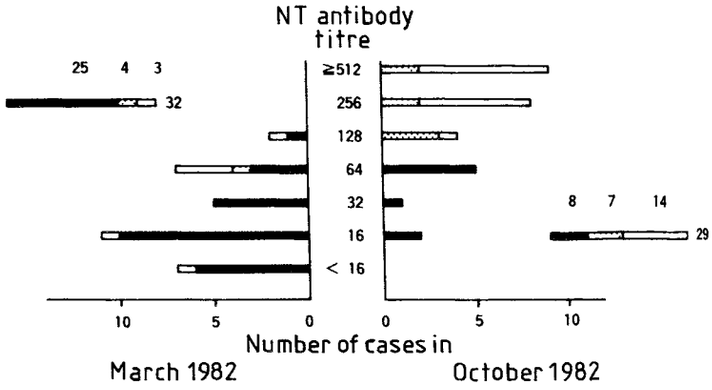

Fig 1—Relation between the herd immunity and the scale of outbreaks.

patients; subclinically infected; uninfected.

TABLE I—RELATION BETWEEN PRE-EXISTING NEUTRALISING ANTIBODY TITRES TO TYPE 3 VIRUS AND INFECTION OR CLINICAL ILLNESS DURING THE OUTBREAKS OF TYPE 3 ROTAVIRUS GASTROENTERITIS

Antibody titre	Number tested	Number infected	Number of patients
<1:16	7	7	6
1:16	13	13	12
1:32	6	6	6
1:64	12	9	8
1:128	6	5	1
1:256	8	2	0
≥1:512	9	2	0

TABLE II—RECURRENCE OF INFECTION AND CLINICAL ILLNESS IN 3 CHILDREN EXPOSED TO 1ST AND 2ND OUTBREAKS OF GASTROENTERITIS DUE TO TYPE 3 ROTAVIRUS

	February, 1981			March, 1982						
Patient no	Age (mo)	Diarrhoea	EM	Age (mo)	Diarrhoea	Vomiting	Fever	EM	Pre-exposure titre	Post-exposure titre
1	4	+	+	18	−	−	−	−	64	256
2	5	+	−	19	+	+	+	NT	64	512
3	8	+	+	22	+	−	−	+	128	NT

EM = electron microscopy findings.

TABLE III—RECURRENCE OF INFECTION AND CLINICAL ILLNESS IN 14 CHILDREN EXPOSED TO 2ND AND 3RD OUTBREAKS OF GASTROENTERITIS DUE TO TYPE 3 ROTAVIRUS

	March, 1982					October, 1982				
Case	Age (mo)	Diarrhoea	EM	Pre-exposure titre	Post-exposure titre	Age (mo)	Diarrhoea	Infection	Pre-exposure titre	Post-exposure titre
4	3	+	+	64	256	10	−	−	512	1024
5	6	+	+	<16	128	12	−	+	128	512
6	6	+	+	32	512	12	−	−	512	256
7	6	+	+	32	128	13	−	+	128	512
8	7	+	+	16	128	14	−	−	512	512
9	8	+	−	16	64	15	−	−	512	512
10	9	+	−	32	128	16	−	−	512	512
11	12	+	+	16	256	19	−	−	512	512
12	12	+	+	<16	256	19	−	−	512	128
13	12	+	−	16	512	19	−	−	256	256
14	13	+	−	16	128	20	−	+	256	2048
15	13	+	+	32	128	20	−	−	512	256
16	14	+	−	<16	128	20	−	+	512	2048
17	14	+	−	32	1024	21	−	−	256	512

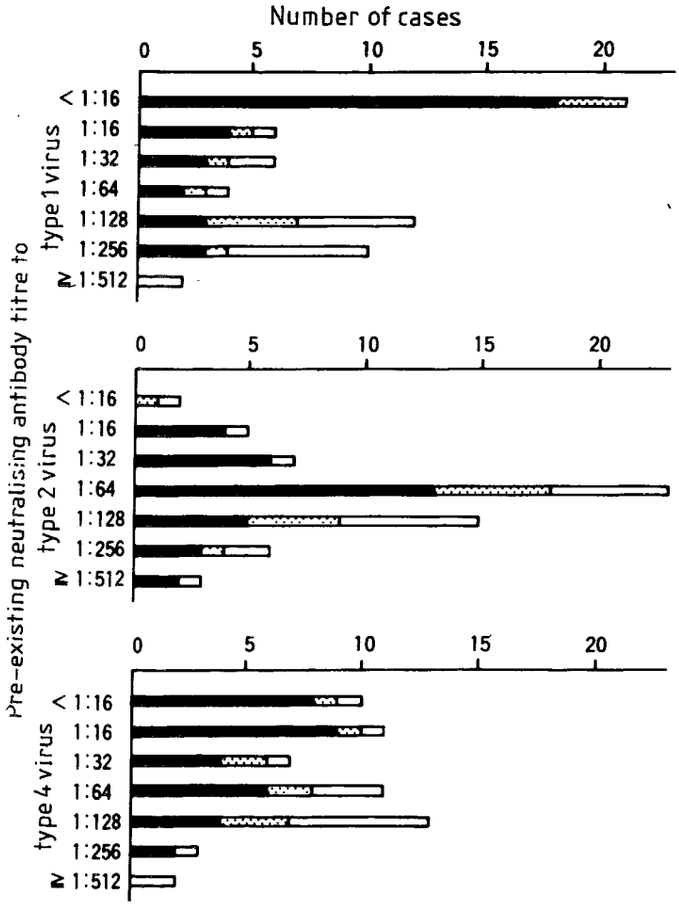

Fig 2—Correlation between pre-existing neutralising antibody titres to heterotypic viruses and infection or clinical illness during the outbreaks of type 3 rotavirus gastroenteritis.

■ patients; ▨ subclinically infected; ▭ uninfected.

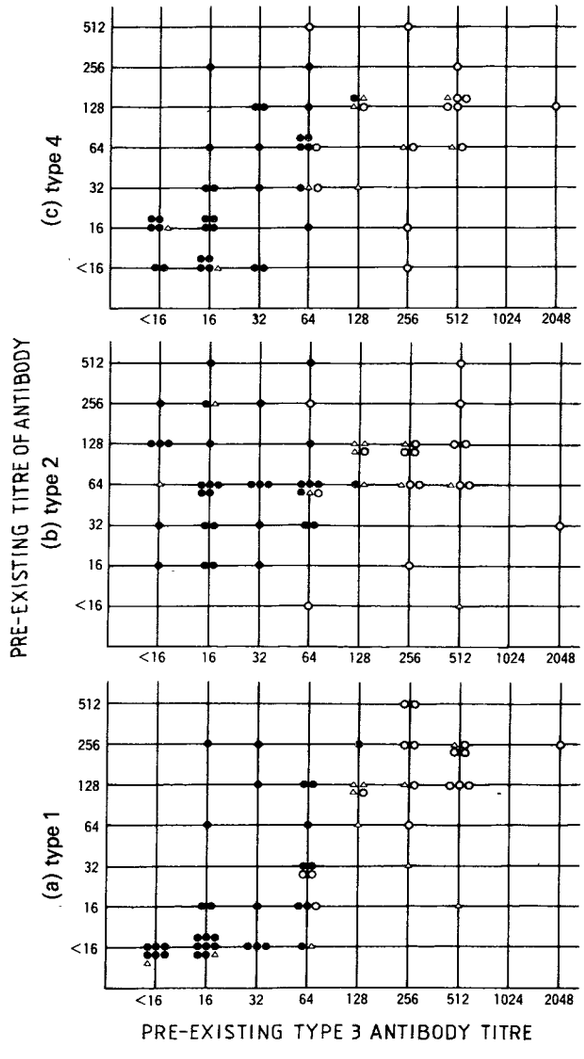

Fig 3—Homotypic (type 3) and heterotypic (types 1, 2, or 4) pre-existing neutralising antibody titres in relation to infection or clinical illness during outbreaks of type 3 rotavirus gastroenteritis.

●patients; △subclinically infected; ○uninfected.

14 of the 25 children with gastroenteritis during the second outbreak were re-exposed to the third outbreak 7 months later. All 14 infants still had high antibody levels (1/128) and were protected against clinical illness, although 4 of them probably had a subclinical reinfection, as suggested by their antibody response (table III).

Influence of Pre-existing Neutralising Antibody Levels to Heterotypic Viruses on Infection or Clinical Illness due to Type 3 Rotavirus

Higher titres of antibody to type 1 or 4 virus seemed to be associated with low attack rates, although the correlation was less clear-cut than the association found for homotypic antibody titres (fig 2). There was no correlation between

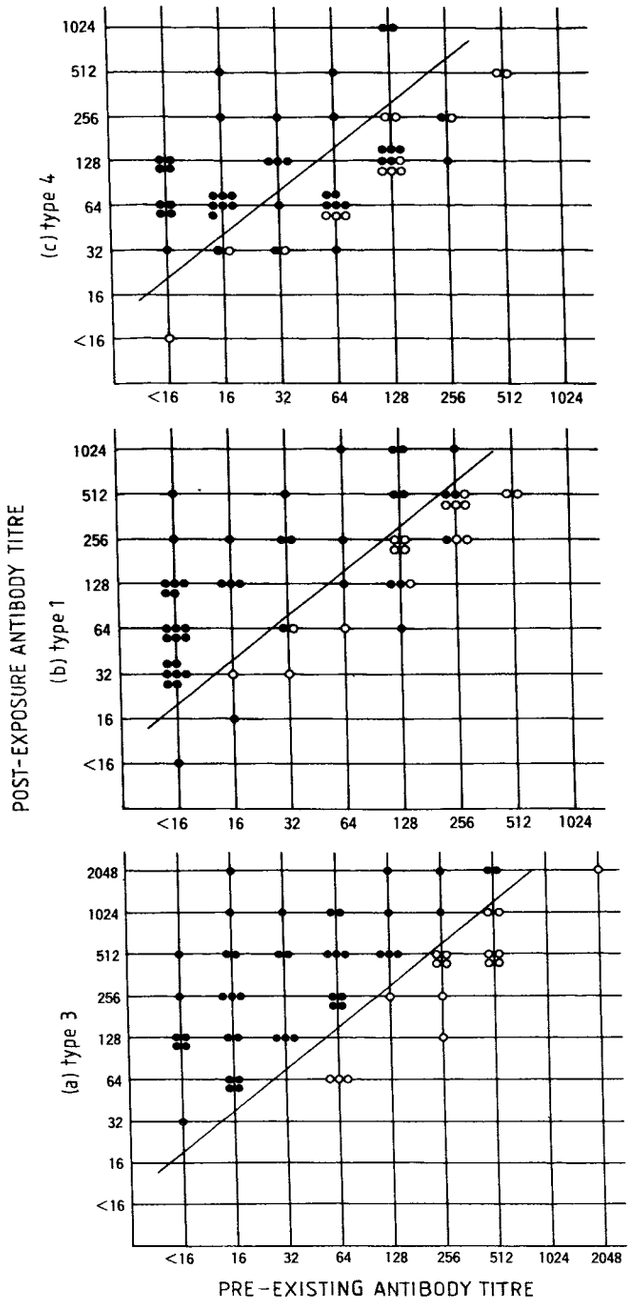

Fig 4—Neutralising antibody against (a) type 3, (b) type 1, and (c) type 4 virus before and after exposure to the outbreaks of type 3 rotavirus gastroenteritis.

●infected; ○uninfected.

anti-type 2 titres and rates of infection or illness. No correlation occurred between anti-type 2 and anti-type 3 titres, and protection against infection or illness depended exclusively on the anti-type 3 titres (fig 3b). A certain degree of correlation was found between anti-type 3 and anti-type 1 or 4 titres (figs 3a and c). However, children with high anti-type 1 or 4 titres but low anti-type 3 titres were not protected against illness. In contrast, high anti-type 3 titres protected against illness irrespective of the level of anti-type 1 or 4 titres.

Heterotypic Antibody Responses Induced by Infections with Type 3 Rotavirus

Most infected infants acquired antibody levels of over 1/128 against homotypic virus (fig 4a). All but 1 of the children seronegative for type 1 or 4 also acquired antibodies against these heterotypic viruses, although the antibody responses were weaker than the homotypic response and the titres ranged from 1/32 to 1/128 (fig 4b and c). Thus, in children infected with type 3 virus concomitant increases in titres of antibody to type 1 occurred in 77% (34/44), to type 4 in 62% (26/42), but to type 2 in only 23% (10/44).

Discussion

Although studies in laboratory animals[7] have revealed that antibody produced locally in the intestine is more likely than serum antibody to be of primary importance in resistance to rotavirus illness, the relation of intestinal immunity to protection against illness in man is not yet clear. However, the presence of pre-existing serum antibodies seems to correlate with protection against diarrhoeal illness due to rotavirus[8-10] and calicivirus.[11] In previous studies the serotype of the reinfecting rotavirus has not usually been established, so some questions about natural immunity against rotavirus gastroenteritis have not been answered. Does homotypic immunity prevent reinfection and resulting clinical illness? If so, for how long? Does cross-protection against heterotypic rotaviruses develop after infection with one rotavirus strain? Answers to these questions should help greatly in the development of an effective strategy for immunisation against rotavirus gastroenteritis. The newer techniques for direct propagation of human rotaviruses in cell cultures enable recovery of rotaviruses from patients with gastroenteritis and determination of the serotype of each isolate.[12-14] We were able to propagate rotavirus isolates derived from the three outbreaks in cell cultures and to identify them as type 3 virus, and from there to analyse immune resistance to rotavirus gastroenteritis in relation to serotype specificity.

Our findings clearly indicate a good correlation between pre-existing titres of neutralising homotypic antibody and protection against rotavirus illness. On the basis of the data shown in table I antibody titres of 1/128 or greater seem to be protective. A titre of 1/128 of neutralising antibodies will be a useful yardstick for monitoring the immune resistance to rotavirus gastroenteritis. The likelihood that this level of antibody prevents rotavirus illness is further supported by the two following observations. First, the difference in the scale of outbreaks could be clearly explained by the difference in level of herd immunity (fig 1). Secondly, frequency of reinfection and clinical illness in children re-exposed to a further outbreak of type 3 rotavirus gastroenteritis was low among children with antibody titres of 1/128 or greater, whereas children with lower levels of antibodies were not protected against reinfection or illness (tables II and III). To our knowledge, this is the first time that evidence has been obtained for recurrence of attacks of gastroenteritis caused by the same serotype of rotavirus. Our findings also indicate that homotypic immunity is short lasting—it may last for half a year but not beyond a year. However, the results have to be interpreted with caution, since the subjects in the study were unique in terms of being members of a closed community. The duration of effective homotypic immunity might well be influenced by epidemiological factors. Frequent exposure to homotypic or heterotypic viruses may result in subclinical reinfection, which contributes to the maintenance of effective immunity by boosting antibody responses.

Several observations have indicated the heterotypic nature of the immune response to rotavirus infection.[8,15,16] Others have also supported the possibility of cross-protection between two antigenically distinct viruses, although there is still controversy over this topic. For example, on the basis of a human volunteer study Kapikian et al[8] suggested that cross-protection could occur. Bishop et al[17] reported that neonatal rotaviral infection protected against severe illness during re-exposure to infection in the postnatal period with presumably a different serotype of rotavirus. Wyatt et al[18] reported that in-utero calf rotavirus infection could induce protection against illness caused by human rotavirus challenge. However, Gaul et al[16] reported that only the homotypic vaccine afforded protection against later challenge with a virulent strain in gnotobiotic piglets. Recently, Offit and Clark[19] found that maternal-antibody-mediated passive protection against rotavirus challenge in newborn mice was dependent on both serotype and titre of antibody.

Since most such studies have been conducted under experimental conditions, we investigated the possibility of development of heterotypic cross-protection against rotavirus gastroenteritis in young children under natural conditions. We examined first the protective ability of heterotypic antibodies and next the possible induction of cross-protection by infection with type 3 rotavirus. There was no relation between pre-existing antibody titres to type 2 virus and protection against illness, whereas attack rates seemed to be inversely related to antibody level against type 1 or 4 virus. However, the apparent protective effect of the heterotypic antibody may be explained simply by the good correlation between antibody levels against type 3 virus and those against type 1 or 4 virus. In other words, humoral immunity against rotavirus gastroenteritis is serotype-specific, although natural infection with type 3 rotavirus often produces concomitant rises in titres of antibodies against type 1 and type 4 virus. Almost all infants sero-negative for type 1 or 4 rotaviruses acquired antibodies to these serotypes, but the titres did not reach positive levels.

Our findings suggest that a rotavirus vaccine should be quadrivalent to produce sufficient protection against group A rotaviruses. However, effective heterotypic immunity may be obtained by a booster dose of a bivalent vaccine that included serotype 2. A booster vaccination would also be necessary to maintain homotypic immunity throughout infancy, since the level of immune response usually decreases with time. Since the purpose of a rotavirus vaccination is the prevention of severe rotavirus gastroenteritis during the first 2 years of life,[1] specific serotypes can be omitted depending on the age-related prevalence of serotype-specific infection in a community.[20] Unlike previous observations of children in Hokkaido[20] the orphans in our study had higher pre-existing antibody titres against serotype 2 virus than against viruses of other serotypes. This finding may indicate that serotype 2 virus strains are prevalent in this closed community, but this serotype seems to be weakly pathogenic since it did not cause outbreaks of gastroenteritis during our study.

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REFERENCES

1 Kapikian AZ, Wyatt RG, Greenberg HB, et al. Approaches to immunisation of infants and young children against gastroenteritis due to rotaviruses. *Rev Infect Dis* 1980; **2:** 459–69.

References continued at foot of next column

DEFECTIVE BRAIN MICROTUBULE ASSEMBLY IN ALZHEIMER'S DISEASE

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Summary Brains obtained within 2–4 hours post mortem and histopathologically confirmed for Alzheimer's disease and non-Alzheimer brains from age-matched controls were examined for in-vitro assembly of microtubules and neurofilaments. Microtubule assembly was observed only in control but not in Alzheimer brains, and neurofilaments were obtained from both types of brain. The microtubule-associated protein tau, which stimulates assembly of microtubules from tubulin, was abnormally phosphorylated in Alzheimer but not in control brain microtubule preparations. Alzheimer brains did not show the presence of any inhibitor of microtubule assembly or any

S. CHIBA AND OTHERS: REFERENCES—*continued*

2. Vesikari T, Isolauri E, d'Hondt E, Delem A, Andre EF, Zissis G. Protection of infants against human rotavirus diarrhoea by the RIT 4237 live attenuated bovine rotavirus vaccine *Lancet* 1984; i: 977–81.
3. Kapikian AZ, Midthun K, Hoshino Y, et al. Rhesus rotavirus: a candidate vaccine for prevention of human rotavirus disease. In: Lerner RA, Chanock RM, Brown F, eds. Vaccine 85 Molecular and chemical basis of resistance to parasitic, bacterial, and viral diseases. New York: Cold Spring Harbor Laboratory, 1985: 357–67.
4. Black RE, Merson MH, Huq I, Alim ARMA, Yunus M Incidence and severity of rotavirus and *Escherichia coli* diarrhoea in rural Bangladesh. Implications for vaccine development. *Lancet* 1981; i: 141–43.
5. Beards GM, Pilford JN, Thouless ME, Flewett TH. Rotavirus serotypes by serum neutralisation. *J Med Virol* 1980; **5:** 231–37
6. WHO Programme for Diarrhoeal Diseases Control. Nomenclature of human rotaviruses designation of subgroups and serotypes. *Bull WHO* 1984; **62:** 501–03.
7. Snodgrass DR, Wells PW Passive immunity in rotaviral infections. *J Am Vet Med Assoc* 1978; **173:** 565–68.
8. Kapikian AZ, Wyatt RG, Levine MM, et al. Oral administration of human rotavirus to volunteers: induction of illness and correlation of resistance. *J Infect Dis* 1983; **147:** 95–106.
9. Black RE, Brown KH, Becker S, Alim ARMA, Huq I. Longitudinal studies of infectious diseases and physical growth of children in rural Bangladesh. II. Incidence of diarrhoea and association with known pathogens. *Am J Epidemiol* 1982; **115:** 315–24.
10. Ryder RW, Singh N, Reeves WC, Kapikian AZ, Greenberg HB, Sack RB. Evidence of immunity induced by naturally acquired rotavirus and Norwalk virus infection on two remote Panamanian islands. *J Infect Dis* 1985; **151:** 99–105.
11. Nakata S, Chiba S, Terashima H, Yokoyama T, Nakao T. Humoral immunity in infants with gastroenteritis caused by human calicivirus. *J Infect Dis* 1985; **152:** 274–79.
12. Sato K, Inaba Y, Shinozaki T, Fujii R, Matsumoto Isolation of human rotavirus in cell cultures: brief report. *Arch Virol* 1981; **69:** 155–60.
13. Urasawa T, Urasawa S, Taniguchi K. Sequential passages of human rotavirus in MA-104 cells. *Microbiol Immunol* 1981; **25:** 1025–35.
14. Hoshino Y, Wyatt RG, Greenberg HB, Flores J, Kapikian AZ. Serotypic similarity and diversity of rotaviruses of mammalian and avian origin as studied by plaque reduction neutralization. *J Infect Dis* 1984; **149:** 694–702.
15. Estes MK, Graham DY. Identification of rotaviruses of different origins, by the plaque reduction test. *Am J Vet Res* 1980; **41:** 151–52.
16. Gaul SK, Simpson TS, Woode GN, Fulton RW. Antigenic relationships among some animal rotaviruses: virus neutralization in vitro and cross-protection in piglets. *J Clin Microbiol* 1982; **16:** 96–103.
17. 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:** 72–76.
18. Wyatt RG, Kapikian AZ, Mebus CA. Induction of cross-reactive serum neutralizing antibody to human rotavirus in calves after in utero administration of bovine rotavirus. *J Clin Microbiol* 1983; **18:** 505–08.
19. Offit PA, Clark F. Maternal antibody-mediated protection against gastroenteritis due to rotavirus in newborn mice is dependent on both serotype and titre of antibody. *J Infect Dis* 1985; **152:** 1152–58
20. Urasawa S, Urasawa T, Taniguchi K, Chiba S. Serotype determination of human rotavirus isolates and antibody prevalence in pediatric population in Hokkaido, Japan. *Arch Virol* 1984, **81:** 1–12.