a severe hearing loss (50 dB in the right ear, 80–90 dB in the left ear), small body size, and mild peripheral pulmonic stenosis. His rubella HAI titer was 1:128; further serologic determinations at 30 and 36 months of age showed no detectable HAI antibody in a dilution of 1:4, nor did he have neutralizing antibody at 30 months.

At 5 years of age he was exposed to, and developed, clinical rubella, with lymphadenopathy and rash. Attempted viral isolation 5 days after the appearance of the rash was not successful but some 3–4 weeks later his rubella HAI titer was 1:512. Subsequently, he experienced a further depression of auditory sensitivity and he now has a severe hearing loss in both ears. He is a highly intelligent child—IQ 137 (Leiter nonverbal test) and there is no question about the validity of the test results.

One further comment pertains to our experience in an epidemiologic study carried out in 1967 by Dr. JOHN GRANT, Maryland State Department of Health. This study was a survey of all the children born in 1964 in several areas in Frederick County, Maryland to determine the number of children with congenital rubella. Of some 600 children screened, 8–10 had defects compatible with congenital rubella, but more than 50% had no rubella HAI antibody. This points out the problem of the limited usefulness of serologic study in the retrospective diagnosis of congenital infection in both the clinical and epidemiologic setting.

Dr. FLORMAN: I think you have touched on the really crucial point, and that is: are these children who are seronegative susceptible to reinfection by wild virus? Your case is very pertinent.

JOSEPH W. ST. GEME, Jr. (UCLA Medical School, Harbor General Hospital, Torrance, Calif.): Is it possible that these children have very low levels of neutralizing antibody?

Dr. FLORMAN: We have not yet tested these children who no longer have detectable HI antibody for the presence of neutralizing antibody.

Dr. HARDY: May I comment on that? Because we have, and there is no neutralizing antibody.

PEARAY L. OGRA (State University of New York, Buffalo, Buffalo, N.Y.): I would like to raise one question in regard to the disappearance of rubella virus antibody in these children. It has been reported in the past that there are children with congenital rubella syndrome who do not have any detectable neutralizing or hemagglutinizing antibody in the newborn period. Is it possible that some of these children who had no detectable HI antibody after 6 months—that the preexisting serum antibody was all transplacently acquired maternal antibody—failed to have an immunological response to start with? Secondly, did you try by any means to identify immunologically the immunoglobulin class with which this antibody activity was associated? Presence of γM antibody would suggest active fetal production rather than maternal transport.

Dr. FLORMAN: As you noticed in our charts, we excluded all determinations on patients' sera except those that were obtained after 6 months of age, because we too were concerned that the determinations done earlier might represent transplacentally acquired antibody. Consequently, all these children had responded with detectable levels of antibody earlier in life, even those who by the age of 2–5 years had lost it.

DOUGLAS E. COX (Wayne State University Medical School and Children's Hospital of Michigan, Detroit, Mich.): Is your twin, which was discordant for congenital rubella and became seronegative before 5 years of age, dizygous by placentation and membranes or by difference in some genetic marker?

(Subsequent communication with the authors (*viz.*, Dr. LOUIS Z. COOPER) has confirmed clear documentation of dizygosity by both criteria.)

8 Rubella: Reinfection in Vaccines and Natural Immunes Exposed in an Epidemic. DOROTHY M. HORSTMANN, HARVEY LIEBHABER, DONALD M. ROSENBERG and SCOTT B. HALSTEAD. Yale Univ. Sch. of Med., and Univ. of Hawaii Sch. of Med.

PEARAY L. OGRA (State University of New York, Buffalo, N.Y.): We have some data which are very similar to what Dr. HORSTMANN has presented today. I think that the basis of herd immunity may really lie in the mechanisms of mucosal immunity, rather than in the circulatory antibody. Presently, we are studying comparative antibody responses in serum and secretions following natural or vaccine-induced rubella virus infection in a large group of children. Preliminary data suggest that although the antibody responses in serum are generally similar, following either type of infection, the responses in the secretions are strikingly different between the two groups. Those children who have been immunized with rubella vaccine usually fail to develop secretory antibody in their nasopharyngeal secretions. On the other hand, the natural disease almost invariably results in γA antibody production in the secretions.

I was wondering if Dr. HORSTMANN had looked at the secretory immune responses among her patients.

Dr. HORSTMANN: We are very much interested in this aspect of the problem, and are currently investigating it, particularly in relation to Dr. STANLEY PLOTKIN's RA 27/3 vaccine. Unlike the HPV 77 derivatives and the Cendehill vaccine, RA 27/3 induces infection and serologic immunity when given intranasally. We do not know whether this vaccine will stimulate a greater secretory antibody response in the nasopharynx than the others, but it seems possible that it might do so. If so, it would have a distinct advantage, for as Dr. OGRA indicated, the superiority of natural over vaccine-induced immunity may be associated with local mucosal antibody and resistance.

HARRY M. MEYER, Jr. (National Institutes of Health, Bethesda, Md.): Four years ago, our reports of rubella virus attenuation to this Society included data indicating that experimental animals immunized with either natural rubella or attenuated virus could undergo modified reinfection after challenge. The following year at these pediatric meetings, we showed that persons with antibodies as a result of earlier natural rubella or vaccination could also experience anamnestic increases in antibody. We noted that these reinfections were subclinical, highly abbreviated from a virologic point of view, and generally occurred in persons with relatively low antibody titers. Since 1967, several groups have confirmed and extended these findings.

This past spring, we had the opportunity to reexamine this matter in considerable detail. Epidemic rubella entered the institution of our earlier studies involving 5 cottages. Each contained susceptible children, vaccinees, and others naturally immune. We examined and collected specimens from each person every day. In brief, 22 of 33 susceptibles were infected; all evidenced signs of rubella. Five of 22 vaccinees and 1 of 66 naturally immune children had subclinical reinfections

as demonstrated by antibody increases. The virologic events were of particular interest:

A. Virus recovery from pharyngeal swabs. With the daily swab collection, the primary rubella cases were shown to shed virus for an average of 17 days. The range was 9–29 days. The profuse pattern of virus excretion in primary rubella is apparent. In contrast, none of the 17 vaccinees resisting reinfection shed virus. Of the 5 vaccinees with an antibody boost only 2 had virus in their pharyngeal secretions. One of these had antibodies when exposed; this child shed virus in 4 specimens. The other was an apparent vaccine failure who never developed antibodies. When reinfected she had 8 virus-positive swabs.

Each positive specimen was assayed for virus content and the quantitative differences were equally striking. The level of excretion in primary rubella ranged from 200 to 80,000 ID_{50}/ml of swab with an average of 6,000. The vaccinee with antibodies had a peak of 50 ID_{50}/ml of specimen. The vaccine failure was intermediate, excreting a maximum of 100 ID_{50}.

B. Virus recovery from heparinized blood. All persons with primary rubella were viremic. In fact, 83% of blood samples collected in the 11 days preceding the appearance of antibodies yielded virus. Comparable specimens from the 5 reinfected vaccinees and the one naturally immune child reinfected were uniformly negative. Again, all positive specimens were assayed for virus content. The level of viremia in primary rubella averaged 800 ID_{50}/ml with a range in individual cases of 10–10,000 ID_{50}.

None of these observations is particularly surprising since similar findings were made in studies of immunity resulting from live polio and rubeola virus vaccination. In terms of degree of resistance one expects attenuated viruses, in general, to evoke lower levels of antibody than their virulent counterparts. This is true of all the live vaccines—those for polio, smallpox, rubeola, mumps, yellow fever, and rubella. Lesser antigenic differences often exist between strains of the same virus. For example, attenuated rubella viruses are not identical and these variations can be correlated with relative resistance to reinfection.

The important issue is to define what may be reasonably expected in the use of the available vaccines. Summing up the experience to date, we see no basis for altering the practical conclusions reached over a year ago: (1) Challenged vaccinees are protected, rarely shed virus, and are not demonstrably viremic; (2) in relation to herd immunity, vaccinated persons with antibody even if reinfected are not likely to participate in the spread of rubella virus in communities; and (3) concerning maternal-fetal infection, it is reasonable to expect significant fetal protection since vaccine-induced antibodies have been demonstrated to serve as a barrier to viremia.

Dr. HORSTMANN: Some of Dr. MEYER's data, as he pointed out, are similar to ours and to those of others. Our whole concern with the problem is that vaccination against rubella is unique, since it is not the *vaccinee* who is the main target, but the *fetus*, some 10 or 15 years hence. It may be that the present vaccination programs will prove effective, but as we gain more experience we tend to be more cautious in predicting an easy victory. The virus turns out to be an unusual agent, virologically and immunologically, and the infection has some strange epidemiologic features. Since there are so many uncertainties, what we need to do at this stage is to follow a number of vaccinated populations closely, and to be alert to the various possibilities that may be in store for us. I do not think that all of the answers are in by any means, nor will they be for some time to come.

9 *Prognosis of Live Infants Who Have Had Intrauterine Transfusions.* WILLIAM COCHRAN, ANN STARK and CELIA SCHULHOFF, Harvard Med. Sch., Boston, Mass. (introduced by Charles Janeway).

RODERIC H. PHIBBS (University of California, San Francisco, Calif.): You can get an erroneous impression of the outcome of a group of intrauterine transfusion survivors if you only examine each child once during infancy or childhood. We have followed a similar though somewhat smaller group, but have examined them every 6 months.

This slide shows the mean and the range of developmental and intelligence quotients at different ages in this group. At 6 and 12 months, and to a lesser degree at 18 months, many performed at a retarded level. As they grew older an increasing number achieved normal performance. All those who have reached 3 years of age are now performing at the normal or above-normal level. If such a group had been tested only once, as you did, when many were less than 1.5 years of age, you might have erroneously concluded that many intrauterine transfusion survivors were moderately or severely handicapped.

In contrast to your findings, we have not found any evidence of severe physical injury due to the transfusions. The majority of our intrauterine transfusions, however, were done under biplane fluoroscopy where the needle can be guided directly into the abdomen, and this may account for some of the differences in findings.

Dr. COCHRAN: In how many of your group did your intrauterine transfusion team not succeed even with their biplane fluoroscopy?

Dr. PHIBBS: Dr. ALAN MARGOLIS, who does all the intrauterine transfusions at our institution, tells me that with the use of biplane fluoroscopy he has never failed to get the needle into the abdomen of the fetus, although he does not always succeed on the first attempt.

Dr. COCHRAN: I agree that more frequent follow-up might easily have changed our DQ and IQ results. Certainly, as already pointed out, our group went from 6 months to 4.5 years and it is well known that any group tested as early as 6 months of age for IQ puts one on shaky ground.

LOUIS K. DIAMOND (University of California Medical Center, San Francisco, Calif.): I am going to draw on our experience in Boston, not San Francisco, with the same patients reported by Dr. COCHRAN, since our Blood Grouping Laboratory was responsible for the amniotic fluid measurements, all the blood group and blood serum tests on mothers and infants, and the intrauterine transfusion procedure carried out by Dr. EASTERDAY, obstetrician, and Dr. UMANSKY, pediatrician, of the intrauterine transfusion team. These women and their infants, here reported by Dr. Cochran, were, therefore, well known to us up to the time of their delivery.

I think Dr. COCHRAN's paper has merit in pointing out that intrauterine transfusion is neither a simple procedure nor one that is without danger. Therefore, it should only be done when clearly indicated, and the patients should be treated with great care, particularly to avoid infection, which I think has occurred a few times in the 150 or more patients that Dr. EASTERDAY and Dr. UMANSKY have transfused.

As to the patients themselves, it is necessary to realize that almost all these infants, based on the past history