Gamma Globulin Prophylaxis; Inactivated Rubella Virus: Production and Biologics Control of Live Attenuated Rubella Virus Vaccines

Discussion on Session V

DR. R. LUNDSTROM, ESKILSTUNA, SWEDEN: The Maternity Welfare Centers in Sweden provide women without a known history of rubella and pregnant up to 14 weeks with convalescent y-globulin, or, when this is not available, ordinary γ-globulin as a prophylactic after exposure to rubella cases. Some women have been treated in spite of appearing with manifest rubella. This is, according to earlier experience, of no benefit in the prevention of congenital defects. The high incidence of rubella defects is apparent in Table 1.

The majority of the women in the group illustrated by Table 2 and 3 reported exposure to rubella within five days prior to the administration of y-globulin and rubella convalescent immune globulin, respectively.

The incidence of defects, commonly ascribed to maternal rubella, in the offspring of the treated women, not presenting with apparent rubella after treatment, did not exceed that which could be expected in the average population; this indicates that the treatment might have been effective in preventing congenital defects. Admittedly, virological control was not available in this series, which seems to be consistent with findings reported by Dr. Sever earlier in this meeting and encourages further investigations under virological control, using material described by Dr. Schiff in his excellent presentation.

DR. V. J. CABASSO, BERKELEY, CALIF: I should like to offer some brief comments on the lot of immune globulin used by Dr. Schiff. This lot was prepared some two years ago at Cutter Laboratories from a pool of plasma procured from Japan. Repeated titrations of this lot in our laboratory, the latest about two weeks ago, gave rubella hemagglutination-inhibiting (HI) titers equivalent to those of several of Cutter's recent lots of regular immune human globulin. These range between 1:2,000 and 1:4,000.

Lots of about the same HI titers were used in a study by a Working Party of the British Public Health Service. In this study, single 750 mg or 3,000 mg doses were given to seronegative subjects, and circulating HI titers were sought in these subjects over a period of several weeks. No rubella antibody level could be detected in the 750 mg group, but detectable levels—1:8 or 1:16—were found in the 3,000 mg group for three weeks, or perhaps four weeks. Translating these dosages in terms of our 16.5% y-globulin preparations, the 750 mg dose would correspond to 4.5 cc and the 3,000 mg dose to 18 cc. The 20 cc dose used in Dr. Schiff's study would therefore correspond to the high dose in the British study.

During the last year, we have been engaged in the development of a high rubella-titer immune globulin, by screening adult donors of natural HI titers of not less than 1:512. Pools of these high-titered plasmas were then fractionated by

mind whenever serum is used in the initial growth of cells that will later be used for vaccine production.

DR. D. T. KARZON, NASHVILLE, TENN: I think it would be instructive for us to hear how many people have been inoculated with this lot of dog kidney propagated rubella vaccine and with any other vaccines produced in canine cell cultures. Many people have elected to continue testing of this vaccine, and I suspect that by now, quite a bit of information must be available.

DR. D. I. MULLALLY, BETHESDA, MD: Althogether there have been 4,155 children who have received rubella canine kidney vaccine. With one exception, reactions have been observed only in the Taiwan study. The one exception, a case of syncope clinically believed to represent anaphylaxis, was reported by Dr. Joan Giles at New York University. This patient was a control subject who did not receive rubella vaccine or any injection but had a venipuncture.

In addition Dr. Veronelli noted one case, presumably of angioneurotic edema, that occurred among 250 children receiving the rubella canine kidney vaccine. The time relationship was such that this reaction appears to have been associated with the vaccine or the vaccination procedure.

In a comparative study involving about 15,000 children, equally divided so that they were immunized with either Cendehill vaccine prepared in rabbit kidney or HPV-77 vaccine prepared in canine kidney, Dr. Gilbert Schiff of Cincinnati observed three cases of urticaria. These three "reactions" appeared within a period of 12 hours following immunization with the Cendehill strain vaccine.

I should like to emphasize the fact that the rubella vaccine manufactured in canine kidney cells is the same vaccine, except for a different virus, as the measles vaccine prepared in the same cell culture system. The experience with canine kidney derived measles vaccine now embraces six million human recipients. There have been no reports of anaphylaxis or other allergic reactions to the measles vaccine.

In conclusion, it would appear that there is not at the present time definitive evidence for any cause and effect relationship between rubella canine kidney vaccine (or any other rubella vaccine) and allergic phenomena such as anaphylaxis, angioneurotic edema, or urticaria. There are underway, of course, additional studies with these vaccines and clinical investigators will be watching closely for other additional "reactions."

DR. S. L. KATZ, DURHAM, NC: I do not think one can compare the virion of measles grown in a cell substrate with the virion of rubella even if grown in the same cell substrate. They are different viruses, and they may acquire different antigens from the cellular membranes. Although I pass no judgment on these reactions described with rubella vaccine, I do not think that we can extrapolate the safety of a rubella vaccine to that of a measles vaccine because they are grown in the same cell. They are different viruses.

DR. K. MCCARTHY, LIVERPOOL, ENGLAND: Is there any possibility that a dog might have formed part of the diet of these children in Taipei?

DR. R. DETELS: In response to Dr. McCarthy, we are told that dog is eaten in Taiwan, but these three children denied having eaten dog.

DR. K. MCCARTHY: It seems to me that there are two things that we worry about in regard to WI-38 cell substrate. First of all, presence of extraneous viral agents; secondly, the possibility of there being human genetic material passed over into the vaccine. I wonder if there is any information about the reasons for aborting that particular embryo that gave rise to WI-38; and if it was from a family, whether we have any information about siblings from the family and whether they are normal?

DR. S. PLOTKIN, PHILADELPHIA: I should like to answer Dr. McCarthy's question. This fetus was chosen by Dr. Sven Gard, specifically for this purpose. Both parents are known, and unfortunately for the story, they are married to each other, still alive and well, and living in Stockholm, presumably. The abortion was done because they felt they had too many children. There were no familial diseases in the history of either parent, and no history of cancer specifically in the families; that is, the maternal or paternal sides. I believe this answers Dr. McCarthy's question.

DR. SABIN: There is no question that a diploid cell that has been carefully tested offersmany, many advantages over a primary cell. But I should like to take exception to two statements made by Dr. Howard Tint. They are not original with him. They have been made before, expressing a certain point of view which I believe needs to be evaluated. The first statement is that the many excellent studies done with the WI-38 strain represent full characterization; the second is that any objection to the use of these cell fluids at the present time for inoculation into human beings is based on emotion rather than reason.

There is no full characterization for any cell line because for everything we do, there is always that hypothetical something for which we cannot test. Just as it applies to other cells now being used on an extensive scale, you can test for the things for which you have a technology, but obviously there is always left a possibility that there is something that you cannot test for. Therefore, the WI-38 cells are no more fully characterized in the light of the intangibles for which there is no technology than other cell lines.

Now, is the objection to use of such cells emotion rather than reason? One of the great efforts that is being made by a number of investigators and the National Cancer Institute here in developing a collaborative program is to determine whether the leukemia sarcoma complex that has now been so well characterized in avian species and in mice may also have its counterpart in human beings. As a matter of fact, if we are going to make much progress in obtaining an answer as to whether human leukemia is caused by virus, it may depend precisely on whether or not we may repeat the basic observation of finding a human sarcoma tumor virus or focus-forming agent on the appropriate kind of human fibroblast cell line. And the appropriate kind of human fibroblast cell line, on the basis of the model systems, would have to be one that on the one hand is leukemia-free and, on the other, has the proper genetic constitution. This, in effect, is the thrust of the study that is being organized.

But if there is a comparable model in human beings (as there well may be) then, on the basis of existing models, one would expect that human embryonic fibroblast cultures, obtained at random, would be the very ones to contain the agent. Furthermore, you would be able to demonstrate the leukemia agent until you had a focus-forming human sarcoma virus of the same antigenic makeup for use in a detection test. The mere statement that careful electron microscopic observations on the cells that have been cultivated reveal no virus-like particles, that might be leukemia particles, does not constitute evidence against it. For example, we have heard here of duck cell embryo cultures infected with rubella virus. Rubella virus multiplied in them, but there are not enough particles to be seen by electron microscopy. Furthermore, the presence of leukemia particles in avian cultures and in murine cultures depends to some extent on the number of serial passages. If one takes early passages of such cultures from stocks that are known to have leukemia in them, you do not necessarily find virus particles.

Therefore, I think that the two statements are not admissible. The statement that they are fully characterized is no