Summary of Informal Discussion of Part II of Genital Herpesvirus

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The discussion concentrated on antigenic aspects of HSV (structural and nonstructural antigens, type-specific antigens, antigenic differences among HSV-2 strains, and antigens common to HSV-2 and cervical cancer) and on antibody responses to HSV (ability to detect specific HSV-2 reactions, role of prior HSV-1 experience, methods of measurement, and frequency of HSV-2 antibodies in cervical cancer).

Dr. Roizman reviewed the relation of antigens to various components of the virus. He presented electron micrographs indicating that viral DNA is spooled around a central cylindrical body which is surrounded by a protein capsid and by an envelope (2). By acrylamide gel electrophoresis, 24 proteins have been detected (3,7). Four proteins (Proteins 5, 19, 23, and 24) are present in the empty capsid and two additional proteins (Proteins 21 and 22a) in the full capsid. It is likely that Protein 21 is the protein that makes up the cylinder on which the DNA is wound. Ten proteins (Proteins 7, 8, and 11 to 18) comprise the glycoproteins present in the viral envelope. These glycoproteins are also present in the membranes of infected cells and are contiguous with host proteins in the membranes. These glycoproteins react with neutralizing antibody and can absorb out such antibodies (5). All the envelope glycoproteins of HSV-1 and HSV-2 cross-react with the heterologous sera on immunoabsorbent columns (6). However, Glycoproteins 7 and 8 appeared to have much greater specificity. A macrolaque HSV mutant which lacks Protein 7 or 8 reacts as an intermediate strain. Dr. Roizman predicted that most specific antigens would be nonstructural rather than structural proteins, on the basis of his observations that the DNA templates for structural proteins have more sequences in common than those specifying nonstructural proteins (4).

Dr. Schneweis noted that most fractions obtained from soluble HSV-1 and HSV-2 antigens after cesium chloride ultracentrifugation were common antigens. However, one fraction appeared specific for each HSV type when reacted with homologous antiserum in immunodiffusion tests. Dr. Schneweis also presented results of the typing of 50 HSV isolates by microneutralization tests, showing that all but two strains fell into distinct clusters.

Dr. Aurelian noted that, during studies conducted in Yugoslavia, two strains appeared to be different from several American HSV-2 strains, but they still resembled HSV-2 more than HSV-1. She also mentioned an early (4-hr) HSV-2 antigen which appeared to react specifically by complement fixation test with sera from women with cervical cancer (1).

Dr. Subak-Shape presented data that showed that both HSV-1 and HSV-2 specify an enzyme with two activities, thymidine kinase and deoxypyrimidine nucleotide kinase. Dr. Rapp commented that, besides the immunogenic differences in the TK of HSV-1 and HSV-2 described by Dr. Wildy, there were also physicochemical differences; e.g., HSV-2 TK is heat stable whereas HSV-1 TK is not. In preliminary observations, Dr. Rapp has detected neutralizing antibodies in the serum of women with cervical carcinoma to HSV-2 TK but not to HSV-1 TK.

As regards ways of obtaining pure, type-specific antigens, Dr. Klein suggested immunoprecipitin approaches similar to those used in the isoantigen field. It is also possible to obtain monoprecipitant antibody since, in immunodiffusion techniques, HSV-1 and HSV-2 type-specific lines can be discerned. It is apparent that several approaches are possible and that the purification of type-specific antigens is crucial to seroepidemiological studies. In this regard, Dr. Rawls noted that, when his new criteria for defining an HSV-2 response were used, significant differences were noted between cancer-bearing and control women (controls being rigorously established with a large number of epidemiological variables). However, although the data have not been completely analyzed, it appears that in Colombia, Israel, and in New Zealand, no differences in HSV-2 antibody frequency were found between cancer-bearing and control women. Dr. Rawls suggested that, on the basis of data he presented earlier in his paper, one possible reason for the inability to detect differences in HSV-2 antibody frequency in some populations may be that HSV-1 antibodies protect sufficiently against HSV-2, so that not enough antigenic load of HSV-2 is available to induce an immune response.

Dr. Klein then asked whether women with prior HSV-1 antibodies may be at greater risk of developing cervical cancer. Dr. Nahmias responded that, although in his series he found 3 to 4 times greater frequency of dual (HSV-1 and HSV-2) antibodies than of HSV-2 antibodies alone in women with cervical cancer, there are two difficulties. One is the reproducibility of the serological test (~85%), the second is that one would expect that about 60% of girls would already have HSV-1 antibodies in their serum by the time of first sexual exposure to HSV-2. Dr. Melnick suggested, however, that prior HSV-1 antibodies might induce a modified virus-cell interaction, perhaps similar to that obtained by in vitro transformation with UV-irradiated HSV-2.

A final note of caution was made regarding serological

[The abbreviations used are: HSV, herpes simplex virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; TK, thymidine kinase.]
assays for herpes simplex viruses in relation to the known cross-reaction of HSV with other members of the herpes-virus group, e.g., HSV and varicella zoster, by complement fixation assays.

References

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