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This Week's Citation Classic®

Nahmias A J, Josey W E, Naib Z M, Luce C F & Guest B A. Antibodies to *Herpesvirus hominis* types 1 and 2 in humans. II. Women with cervical cancer. *Amer. J. Epidemiol.* 91:547-52, 1970. [Depts. Pediat., Preventive Med., Gynecol. and Obstet., and Pathol., Emory Univ. Sch. Med. and Grady Mem. Hosp., Atlanta, GA]

This seroepidemiological study demonstrated further evidence for an association between genital herpes simplex virus infection and cervical neoplasia and suggested more investigations were needed to substantiate a causal relationship. [The *SCI*® indicates that this paper, cited in over 220 publications, is among the most cited for this journal.]

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Much of the data comprising this report had been obtained three years earlier, and we delayed submission until we were more confident of the technology employed. It is somewhat amusing to me that this report, as well as seroepidemiological studies by two other groups, has been erroneously cited as being the *first* suggestion of a relation between genital herpes simplex virus (HSV) infection and cervical neoplasia. It is like saying that the first evidence for a relation between Epstein-Barr herpesvirus and Burkitt lymphoma was made by serological means! The story is quite different.

In 1964, I was clinically involved with a baby with generalized herpes. In trying to track down the source of infection, I found that the mother had had a cervical lesion and that Z. Naib, our cytopathologist, had detected cellular changes suggestive of herpes on a Pap smear. We confirmed a herpetic cervicitis in the mother by viral isolation. Together with W. Josey, we then confirmed that what Naib was detecting cytologically in many other women was indeed due to HSV, and we made the original observation that HSV frequently affects the cervix asymptomatically. Our group also noted that women with genital herpes had a higher frequency of cervical neoplasia. In order to demonstrate the possible oncogenicity of the genital virus in animals, we inoculated human genital and nongenital HSV isolates intravaginally in mice and found that the genital viruses were much more virulent than nongenital isolates.

By coincidence, W. Dowdle of the Centers for Disease Control is my neighbor. Together with a graduate student, Bill Paul, Dowdle had confirmed by neutralizing potency (pn) assays the earlier observations of K. Schneweis[1] and G. Plummer[2] that there were antigenic differences among herpes simplex viruses. It was during a leisurely Sunday conversation, in between mowing our lawns, that Dowdle and I thought it would be of interest to see whether genital strains found to differ in mice would also differ by antigenic type. It was one of my greatest scientific thrills to find out that all of the genital HSV isolates we initially tested antigenically were type 2, whereas nongenital isolates were type 1.

We now had a potential means for detecting HSV-1 and HSV-2 antibodies by the same pn assay, using known type 1 and type 2 strains and unknown sera. However, when applied to sera of cancer-bearing and control women, we found that many of the cancer sera gave reactions in a zone in between that found to separate type 1 and type 2—"intermediate" antibodies. Although possibly a result of technical problems, an alternative explanation was that such intermediate antibodies represented dual antibodies, i.e., antibodies to both HSV types. We therefore aimed our efforts over the next two years at differentiating between these two alternatives in both animal and human studies.

We had reported some of our earlier findings relating genital herpes to cervical neoplasia from 1966 to 1968 and reviewed them at the international virology meetings in Helsinki during the summer of 1968. A few months later, a paper appeared in *Science* by the Baylor group whereby, using a plaque assay, "type 2 antibodies" were reported to occur in higher frequency in the sera of women with cervical neoplasia than in controls.[3] It is of some interest that these workers did not appear to be aware of the problem of dual antibodies and did not cite our earlier work.

Much still remains to be done to prove the causality of genital herpes in cervical neoplasia. Results of our prospective study suggest that primary genital HSV infections are more likely to be important, and other studies indicate that either HSV-2 or HSV-1 may be involved.[4] Furthermore, several groups are now incriminating papilloma viruses as potentially oncogenic agents in the cervix. In the long run, the final proof of causality may have to come by showing that women protected from genital herpes and/or papilloma viruses would have a lower frequency of developing cervical neoplasia in comparison with nonprotected women.

I hope that these comments provide further support for the well-appreciated fact that many reports, which seem so well thought-out in their published form, are really a result of chance events to the prepared mind.

1. **Schneweis K E.** Serologische Utersuchungen zur Typendifferenzierung des Herpesvirus hominis. *Z. Immun. Exper. Ther.* 124:24-48. 1962. (Cited 95 times.)
2. **Plummer G.** Serological comparison of the herpes viruses. *Brit. J. Exp. Pathol.* 45:135-41. 1964. (Cited 115 times.)
3. **Rawls W E, Tompkins W A, Figuero M & Melnick J L.** Herpesvirus type 2: association with carcinoma of the cervix. *Science* 161:1255-6. 1968. (Cited 215 times.)
4. **Nahmias A, Adelusi B, Naib Z & Muther J.** Changing concepts on the relation of genital herpes and cervical cancer. (Grundmann E, ed.) *Cancer of the uterine cervix.* Stuttgart: Gustav Fischer Verlag, 1985. p. 141-9.

