

Statement of J. Thomas Cox, MD
Regarding
Hearing on Human Papillomavirus and Cervical Cancer

Chairman Souder, members of the House Subcommittee on Criminal Justice, Drug Policy and Human Resources, my name is John Thomas Cox, MD. I am Director of the Women's Clinic at the University of California in Santa Barbara, Past-Chair of the Steering Committee for the National Cancer Institute sponsored ASCUS/LSIL Triage Study (ALTS) and Secretary of the American Society of Colposcopy and Cervical Pathology. I want to express my thanks for providing me the opportunity to present a clinical perspective on the issues related to human papillomavirus and cervical health as I see it in 2004.

Cervical cancer prevention: Where are we in 2004?

I had the privilege of sharing information of cervical cancer screening and human papillomavirus at a 1999 hearing of the House Subcommittee on Health and the Environment. Since that time there has been a "sea change" in cervical cancer screening recommendations and in management of women with abnormal Pap tests. As a result, women in the US and, to some extent, worldwide, will benefit by improved recommendations that focus on detection of the cause of cervical cancer, HPV, and not solely on often subjective cervical cellular changes. However, it must be remembered that the Pap test has successfully decreased cervical cancer incidence approximately 1% per year over the past 26 years. Cervical cancers are now uncommon, the annual incidence per million women ranging from 8 to 14 for squamous cell cancers and from 0.7 to 2.7 for cervical adenocarcinoma. In 1949, the year that Pap smear screening was introduced in the US the 2004 equivalent of 50,000 cases of cervical cancer occurred. Instead, the Pap and subsequent treatment of successfully identified cervical cancer precursors has reduced this rate to 12,200 and is steadily declining yearly. Although cervical cancer has not yet been entirely eliminated in the US, it

is surely not an epidemic as some would lead all to believe. However, the potential to nearly eliminate cervical cancer is on the near horizon. For that to happen, we, as educators, as policy makers, and as caregivers must work together, with our only interest being in the well-being of all women. This requires a solid commitment to appropriate education of our youth, to provision of resources that provide access for the best up-to-date cervical cancer screening for all women in the US and for provision of HPV vaccines for all children when they become available. We must not forget that the majority of women who get cervical cancer are those who have either never has a Pap test, or have had one or more Paps but have not had them at recommended intervals.

Commitment to appropriate education of our youth

HPV is the most common sexually transmitted disease in America. Seventy-five to 80 percent of sexually active Americans will be infected with HPV at some point in their lives – meaning that anyone who has ever had sexual relations has a high chance of being exposed to this virus. HPV is sexually transmitted and depending upon the location of HPV induced lesions can be transmitted despite consistent condom use. HPV is asymptomatic and as with most viruses, there is no direct treatment of the virus yet available. However, the immune system most commonly suppresses or eliminates HPV, with the infection usually becoming undetectable within 6 months to 2 years. In rare instances, persistent infection with certain types of HPV can cause cervical cancer. HPV must be present for cervical cancer to develop, however, it is critical to remember that the converse is not true – infection with HPV does NOT mean that a woman will eventually get cervical cancer. Only a small proportion of women infected with HPV will get cervical cancer – for cervical cancer is an uncommon consequence of HPV infection. However, many will use these statistics related to transmissibility and the connection between HPV and cervical cancer to promote abstinence until marriage on the basis of fear. Others will point to the high rate of spontaneous suppression of HPV as reassurance that the almost ubiquitous infection rate of HPV does not justify over-reaction and the fact that most studies show

decreased rates of genital warts and cervical cancer amongst women whose partner(s) consistently use condoms. Unfortunately, fear messages based upon overstating the risk of HPV and understating the protection provided by condoms threatens to undermine the tremendous progress made to lower teen pregnancy and STD rates.

What should the educational messages be? There is no question that the more partners one has and the earlier that one begins sexual activity, the higher the risk for infection with any of the sexually transmitted diseases. It is also true that diligent condom use does not consistently prevent HPV transmission, despite decreased rates of genital warts and cervical cancer noted with such use in most studies. So what should education be for our children if we are to best prepare them for their years as adults? Should we teach them that the only sure way of preventing all STDs is to abstain from intercourse until marriage and not discuss protective measures just because not all are definitively prevented? Or should we be realistic and pragmatic, taking into account the reality of people's lives. We are not just discussing the education of children but the preparation of our children to be adults. The median age for marriage in the US continues to rise for both men and women. In 1970 the median age for first marriage was 20.8 years for women and 23.2 years for men. By 2000 these ages had risen to 25.1 years for women and 26.8 years for men. The median age of puberty is 13. Throughout history, virginity (for women) until marriage has been secured primarily by either very early marriage of women soon after puberty, or by sequestering women in strictly controlled separation of the sexes until marriage. That these approaches do not exist in most of the US, nor would they ever be acceptable to a free society, is not arguable. As the "Family Life Education Act of 2001" (H.R. 3469) so correctly stated "Comprehensive sexuality education programs respect the diversity of values and beliefs represented in the community and will compliment and augment the sexuality education children receive from their families". Can we realistically promote abstinence-only in the majority of adults until their late 20s? Sex education must teach both the

positives of abstinence until marriage and educate how best to minimize risk for the majority who will undoubtedly at some point choose otherwise. Short of abstinence, condoms remain the best protection against a range of sexually transmitted diseases, including HIV. There is no place in government legislation for regulation of educational or medical policy that falls far outside the arena of the majority of medical and educational research and thought. What government can do is provide funds that make sure that the best messages are taught that encourage young people to delay the onset intercourse and at the same time prepare them with the tools needed to best protect themselves and their partner from sexually transmitted diseases once they do become sexually active. That is the only realistic protection. In my view, the language of the Family Life Education Act, if not distorted to favor one viewpoint over another, provides that balance. The Act lists the following as requirements for a program of family life education:

- (1). Is age appropriate and medically accurate
- (2). Does not teach or promote religion
- (3). Teaches that abstinence is the only sure way to avoid pregnancy or sexually transmitted diseases
- (4). Stresses the value of abstinence while not ignoring those young people who have had, or are having sexual intercourse
- (5). Provides information about the health benefits and side effects of all contraceptives and barrier methods as a means to prevent pregnancy
- (6). Provides information about the health benefits and side effects of all contraceptives and barrier methods as a means to reduce the risk of contracting sexually transmitted diseases, including HIV/AIDS
- (7). Encourages family communication about sexuality between parent and child
- (8). Teaches young people the skills to make responsible decisions about sexuality, including how to avoid unwanted verbal, physical and sexual advances and how not to make unwanted verbal, physical and sexual advances

- (9). Teaches young people how alcohol and drug use can effect responsible decision making.

However, it is imperative that the language of this Act not be distorted to favor one approach over another. While the decision to teach sex education and the content of such education is left to the states and to the individual school districts, the influence of the federal government via funding provided for such programs undeniably influences these prerogatives. Funding for abstinence only education has increased 3000% since the 1996 federal entitlement program sponsoring abstinence-only messages. Promoting an imbalance in sexual education by exclusive funding of abstinence-only education puts the population at-risk for serious consequences secondary to lack of preparation for the inevitable time that one will become sexually active. Additionally, fear messages implicit in statements that over-emphasize medical risks may place healthy sexual relationships hostage to fear. In the 2004 State of the Union address the President proposed "a grassroots campaign to help inform families about these medical risks...We will double federal funding for abstinence programs, so schools can teach this fact of life: Abstinence for young people is the only certain way to avoid sexually transmitted diseases." The president's new budget includes an additional \$270 million for programs to encourage teens to abstain from sex. If, in contrast, the new budget included this amount for comprehensive sex education rather than one with an abstinence-only approach, the interests of all Americans, rather than only a special interest group, would be furthered.

Since the late 1980s, both the political context surrounding sexuality education and actual teaching approaches have changed considerably. That abstinence-only education is becoming more common as a result of increased federal funding for abstinence-only programs is undeniable, and despite the Family Education Act pronouncement that family life education "not teach or promote religion", there is no question that some religions have been in the forefront of promoting abstinence only education. Whereas only 2% of sex education classes

in the US taught “abstinence only” messages in 1988, 23% did so in 1999. These programs often exclude basic information related to puberty and reproduction, in addition to providing little information on pregnancy and STD prevention other than by abstinence. This approach has been promoted by the federal government despite evidence to the contrary that abstinence only programs show little success in delaying onset of sexual activity until marriage but do contribute to inadequate preparation to avoid pregnancy and STDs when they do become active. That rules and regulations are increasingly interfering with what teachers think should be taught is apparent from data that 90% of teachers believe that students should be taught about contraception but 25% are barred by regulations from doing so.

Most of the trusted medical institutions in the US support comprehensive sex education. This includes the American Medical Association, the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, the American Public Health Association and the American Nurses Association. Additionally, the majority of parents want their children to have comprehensive sex education. I urge you as influential members of the Congress to make decisions regarding sex education that are supported by the majority of Americans and by knowledgeable, respected institutions.

Commitment to providing the best available screening

Cervical cancer is nearly entirely preventable because the cancer occurs on a skin surface that is easily accessible for evaluation, risk of presence of the precancer phase is detectable by the Pap test and by HPV testing and the natural history of progression from precancer to cancer is one that is usually quite long over many years to decades. That cervical cancer should be preventable in most circumstances makes every cervical cancer even more tragic. Only an all-out commitment by private and public payers to provide the best screening available for all women can reduce the burden of this tragedy.

Promoting access to the best cervical screening

The majority of cervical cancers continue to occur in women receiving either no, or inadequate, cervical screening. Therefore, education, outreach and access for all women to equal protection from cervical cancer will provide the maximum benefit in reduction of cervical cancer incidence and mortality. Cervical cancer not infrequently strikes women of late child-bearing age, disrupting families and society much more than many other cancers that occur with highest frequency in the elderly. Wise investment by government in a program of cervical cancer prevention is, therefore, both morally right and economically sound. It is likely that women fail to get adequate cervical screening as a result of a complex milieu of cultural, societal and educational factors. A substantial commitment to understanding the reasons for failure to attend screening is necessary in order to overcome these barriers.

Education about the necessity for the presence of HPV in the etiology of cervical cancer and the commonness of this virus must be balanced with reassurance that attendance at recommended screening provides protection from serious outcome for most. Education must extend to the health care provider as well, for outreach and recruitment to responsible preventative care is doomed to failure without a well-informed and empathetic health services sector. Education must include discussion of the sexually transmitted nature of HPV and the relationship of true Pap test abnormalities with an STD, and must be done without prejudice and with great care, compassion, and reassurance.

A More Efficient Screening System

When I last spoke to a Congressional Subcommittee on this subject I emphasized a number of points that must occur before a more efficient screening system would come to fruition. Many of the limitations to the system that I spoke of then have subsequently been corrected by new national screening and management guidelines issued by the American Cancer Society (ACS), the American College of Obstetrics and Gynecology (ACOG), and the American Society for Colposcopy and Cervical Pathology (ASCCP). These include the

optimal age to begin screening, the optimal interval for screening, provision of the best technologies for improved screening, and provision of the most objective and efficient management of women with equivocal Paps.

1). *Optimal age to begin screening:* In order to provide the safest and yet cost-efficient coverage, it was imperative to redirect a large concentration of our cervical cancer screening resources to populations at greatest risk and least likely to be traumatized unnecessarily by medical intervention. New national guidelines accomplished this feat by recommending that cervical cytology screening not begin until age 21 or within 3 years of first intercourse, whichever comes first. These parameters replaced previous guidelines that called for first Pap test at age 18, or at the time of first intercourse. This does not negate the importance of continued medical interaction with young people who have begun sexual activity but do not yet need cervical screening, for it remains very important to test young sexually active women for other STDs and to provide contraceptive services. However, as we learned more about the high-prevalence of transient HPV infections in very young women and the long natural history required for the development of serious cervical disease it became increasingly clear that the previous recommendation to begin Pap screening no later than age 18 was inefficient and wasted resources better spent on cervical cancer screening of older women at greater risk of having persistent precancer requiring treatment.

(2). *Optimal screening interval:* Annual Pap tests have been the standard in the US for over 50 years, this frequency driven by concerns over false-negative Paps, medicolegal liability and the improbability of being able to accurately predict which women are really low risk on the basis of mostly non-verifiable sexual history factors. These concerns served as the major impediment to implementation of prolonged screening intervals. However, the advent of new technologies that improve the sensitivity and efficiency of detection of cervical disease has fostered guidelines that promote longer screening intervals on the basis of decreased risk for missed cervical precancer and cancer. The new technologies of greatest benefit are liquid-based thin-layer

cytology and HPV testing. The 2002 American Cancer Society cervical screening guidelines, in recognition of the improved sensitivity of liquid-based Paps, recommended that women up to age 30 have cervical screening only every 2 years if liquid-based, in contrast to annually if a conventional dry Pap smear. Decreasing the number of screens in a woman's life is advantageous if the risk of missing serious disease is not increased because it becomes less likely that transient unimportant HPV changes will be detected. For women after the age of 30 the opportunity for extending screening intervals is given in both the ACS and the ACOG guidelines, which recommend Pap testing every 2 to 3 years for women of this age having 3 consecutive normal Paps, or every three years for women having a single screen that was negative for high-risk HPV and normal on a Pap. The age of 30 was selected as the beginning age for combined screening with HPV testing and the Pap test because women over the age of 30 are less likely to have transient HPV and more at-risk for HPV-induced precancer. The 3-year interval recommended by ACS, ACOG and the recently published "interim guidance" on the use of this "super screen" was based on the nearly 100% negative predictive value of combined testing for precancer and cancer. Additionally, women negative for high-risk HPV are not at-risk for cervical cancer over the next few years, providing a longer period of reassurance than cytology alone. This extended period of protection is even more important amongst women attending government-funded clinics, because regular attendance for recommended cervical screening is often less guaranteed in this setting. Investment in providing the best protection for women at all economic levels is likely to provide substantial return.

These new technologies and guidelines on their use now provide the opportunity to make a significant impact on both the loss of life and on the inefficiency of the cervical cytology screening program if we have the will and the foresight to integrate the best that these technologies provide. If we do not, the present impasse in further reduction in cervical cancer may remain. Much not only depends upon the willingness of third-party payers to cover appropriately effective emerging technologies, but also upon a full understanding by clinicians

of their potential and the willingness to discuss the new methods with their patients.

3). *Providing the most objective and efficient triage of women with equivocal Paps:* When I last spoke before a Congressional Subcommittee data was emerging from the NCI/ALTS Study that indicated that testing for HPV was the most sensitive and efficient management of women with the Pap interpretation of atypical squamous cells of undetermined significance (ASCUS) when obtained from a liquid-based Pap. However, I emphasized that, despite favorable data, the one FDA-approved HPV test, Hybrid Capture 2, was yet to be covered by most third-party payers in the management of women with this Pap reading. This changed dramatically with publication of the ASCCP Guidelines for the Management of Women with Abnormal Cervical Cytology in 2002, which recommended that HPV testing was the preferred management option for women with ASCUS when derived from liquid-based cytology. Now most third party payers cover the cost of HPV testing as recommended by the guidelines. The primary exception is the government-funded clinics under the Title X program, which have continued to fund only management options that would appear to be less protective.

(4). *Cost-benefit analysis:* Cost of providing improved technologies for cervical screening is usually measured in terms of dollars spent per year of life saved. Considering the relative rarity of cervical cancer, the costs always appear on the high side, although much lower than many other interventions. In contrast to measuring only dollars spent for deaths prevented, a much fairer model is one that takes into account all the factors of cervical cancer screening that affect women's lives. This would encompass quality-of-life issues associated with earlier detection of disease, including reproductive implications, and reductions in invasive treatments, patient anxiety and loss of time from work and childcare. Women have a right to be routinely informed of these issues and to participate in decision-making regarding their health choices.

Provision of Vaccines for all Children

Cervical cancer will nearly be eliminated during the lifetime of many attending this meeting. Its demise will come on the heels of the improvements in screening and management we have discussed today, and on the availability in the near future of vaccines against HPVs 16 and 18. If introduced worldwide, vaccination against HPV 16 alone could prevent over 50% of the nearly one-quarter million deaths that occur annually from cervical cancer. A quadravalent vaccine including types 6, 11, 16 and 18 could theoretically prevent 90% of genital warts and 75% of cervical cancers. The potential is not only in reduction of morbidity from genital warts and cervical cancer, and mortality from the latter, but in the possibility that physical, psychological, and financial costs associated with screening, follow-up, and treatment should be significantly decreased. Two different categories of vaccines are presently under development or testing: prophylactic and therapeutic. Prophylactic vaccines are directed to preventing infection from occurring, whereas therapeutic vaccines are designed to either eliminate HPV infections in patients already infected with HPV, or to kill high-grade precancer and invasive cancer cells. Prophylactic HPV vaccines will need to be administered before infection in order to elicit neutralizing antibodies that would either inhibit attachment or entry. Because HPV is easily and frequently transmitted soon after sexual debut, the target population for prophylactic HPV vaccination will necessarily be children that have not attained the age of sexual maturity. Recent studies offer promise that prophylactic HPV vaccines against these types may be 100% effective in preventing both infection with the types included in the vaccine and the precancer that such types may induce.

Again, thank you for the opportunity to address these issues. The war against HPV and cervical cancer will be won. All we have to do is hold the course steady by appropriately educating our youth, providing the best protective cervical screening available for all women, and providing HPV vaccines to all children once these vaccines become available. I will be pleased to answer any questions that you may have.