

HPV VACCINES MECHANISMS OF ACTION IN WOMEN

Endocrine Influence
HPV Pre-Testing
Immune System Involvement

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Premise

Data & peer reviewed analysis exposes endocrine influence in the stimulation of the human papillomavirus in women previously exposed and in post vaccination.

Expounding the analysis presented in the 3.06.10 FDA Listening Session for the following subgroups and the need for HPV Screening

- Athletic Girls
- Overweight Girls
- Vaccination During Paramenstrum

Menstrual Cycle Studies

- ▣ PubMed.gov
Arch Physiol Biochem. 2001 Oct; 109(4):383-7.
Impact of stress, gender and menstrual cycle on immune system: possible role of nitric oxide.
- ▣ Journal of Reproductive Immunology
Volume 50, Issue 2, Pages 151-159 (May 2001)
Influence of menstrual cycle on NK activity
- ▣ PubMed.gov
Acta Obstetrica et Gynecologica Scandinavica
1976, Vol. 55, No. 4, Pages 297-304
Histamine Metabolism During the Menstrual Cycle
- ▣ NeuroScience Inc.
Neuroimmunology of Autism Spectrum Disorder

Menstrual Cycle Studies

- Effect of the Menstrual Cycle and Hormonal Contraceptives on Human Papillomavirus Detection in Young, Unscreened Women
<http://www.ncbi.nlm.nih.gov/pubmed/20567170>
- Effects of estrogens and androgens on erythrocyte antioxidant superoxide dismutase, catalase and glutathione peroxidase activities during the menstrual cycle.
<http://www.ncbi.nlm.nih.gov/pubmed/11115771>

Research Data Presented on
Menstrual Cycle Evaluation on
Hormones, HPV & Histamine
Interaction from the
March 2010 FDA Presentation

Human Papillomavirus Studies

- Obstet Gynecol. 2008 Nov; 112(5):979-89.

Prevalence of HPV Infection Among Females in the United States

CONCLUSION: HPV is common among females in the United States. Our data indicate that the burden of prevalent HPV infection among females was greater than previous estimates and was highest among those aged 20 to 24 years. However, *the prevalence of HPV vaccine types was relatively low.*

- J Infect Dis. 2005 Jan 15; 191(2):182-92. Epub 2004 Dec 10.

A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women.

CONCLUSIONS: The cumulative prevalence of HPV infection in sexually active adolescent women is extremely high, *involves numerous HPV types,* and frequently results in cervical dysplasia.

- Obstet Gynecol. 2008 Nov; 112(5):979-89.

Prevalence of high-risk human papillomavirus among older women.

CONCLUSION: In this nationally representative population, nearly 1 in 16 women aged 57-85 was found to have high-risk HPV, and prevalence was stable across older age groups.

Research Data

- Histamine Metabolism During the Menstrual Cycle
Acta Obstet Gynecol Scand. 1976;55(4):297-304.
- Possible role of histamine in pathogenesis of autoimmune diseases: Implications for immunotherapy with histamine-2 receptor antagonists,
Medical Hypotheses, Volume 39, Issue 4, Pages 349-355, H. Nielsen, J. Hammer ,
- Cadernos De Saude Publica, Rio de Janeiro, 21(4): 1006-1015, jul-ago, 2005
- Journal of Clinical Microbiology, January 2005, p. 376-381, Vol. 43, No. 1
- Journal of Medical Virology, Vol 61 issue 1, pp 70-75 (2000)

HPV Replication vs. Stimulation

- ▣ Study on How HPV Propagates
- ▣ Ampheregulin Stimulation of HPV
 - VAERS Report on Ovarian Cancer Death
 - Overstimulation of HPV Cells in the Ovaries
 - PCOS – Poly Cystic Ovarian Syndrome & HPV

Study on How HPV Propagates Amphiregulin

"HPV infections occur frequently in sexually active individuals; however, only a minority of infected women actually develop cervical cancer (7). Thus, additional environmental and/or hereditary factors are involved in malignant progression. A number of other sexually transmitted diseases frequently accompany infection with HPV (8, 9) and cause acute or chronic inflammation within the cervical mucosa"

"These results demonstrate that transfection and immortalization of cervical epithelial cells with HPV-16 or -18 DNA induces sensitivity to growth stimulation by IL-1 α and TNF- α ." However, growth stimulation by these cytokines is not limited to cells containing HPV DNA. Previous studies have shown that several proinflammatory cytokines (IL-1 α , IL-6, or TNF- α) stimulate proliferation of carcinoma cell lines derived from several different tissues (24, 33, 34) including cervix (35). Thus, proinflammatory cytokines might act as paracrine or autocrine growth factors in promoting malignant progression."

Proc. Natl. Acad. Sci. USA Vol. 92, pp. 2840-2844, March 1995 Cell Biology, Interleukin 1 α and tumor necrosis factor α stimulate autocrine amphiregulin expression and proliferation of human papillomavirus-immortalized and carcinoma-derived cervical epithelial cells, <http://www.pnas.org/content/92/7/2840.full.pdf>

Amphiregulin Stimulation of HPV

"Amphiregulin is a member of a large family of polypeptide growth factors that bind and activate the EGF receptor (reviewed in ref. 27). Amphiregulin was originally purified from MCF-7 breast carcinoma cells (28), but it has also been detected in normal tissues, including ovary, placenta, colon, and epidermis (18). Our results implicate amphiregulin as an important autocrine factor that mediates growth stimulation of HPV-immortalized cervical cells by IL-1 α or TNF- α .

Autocrine amphiregulin expression is important in supporting autonomous growth of cultured epidermal keratinocytes (18) as well as colon and breast carcinoma cell lines (29, 30). Furthermore, amphiregulin is often overexpressed in malignant colon or mammary tissue relative to the normal epithelia (31, 32), suggesting that altered regulation of this growth factor may contribute to malignant development. Our results demonstrate that two proinflammatory cytokines, IL-1 α and TNF- α , stimulate proliferation of cervical cells via autocrine induction of amphiregulin.

Proc. Natl. Acad. Sci. USA Vol. 92, pp. 2840-2844, March 1995 Cell Biology, Interleukin 1 α and tumor necrosis factor α stimulate autocrine amphiregulin expression and proliferation of human papillomavirus-immortalized and carcinoma-derived cervical epithelial cells, <http://www.pnas.org/content/92/7/2840.full.pdf>

VAERS Report

Ovarian Cancer Death

- ▣ VAERS ID: [391339](#)
- ▣ Age: 16.0
- ▣ Submitted: 2010-06-23
- ▣ Entered: 2010-06-24, Days after submission: 1
- ▣ Vaccination HPV 4
- ▣ Manufacturer - Merck & Co. Inc.
- ▣ Symptoms: [Death](#), [Ovarian cancer](#)
- ▣ Write-up: Information has been received from a physician via CSL as part of a business agreement (manufacturer control # 20100617KC1) concerning a 16 year old female who on an unspecified date was vaccinated with a dose of GARDASIL (lot # not reported). After the GARDASIL vaccination, 3 months later, the patient died of ovarian cancer. The patient was treated at a women's hospital. The physician stated that there was no causal relationship between the vaccine and death. Additional information has been requested.

VAERS Report

Ovarian Cancer Death

- VAERS ID: [376734](#)
- Age: 17.0
- Submitted: 2010-01-12
- Vaccinated: 2008-11-15
- Entered: 2010-01-13, Days after submission: 1
- Vaccination HPV 4
- Manufacturer: Merck & Co. Inc.
- Symptoms: [Abdominal distension](#), [Nuclear magnetic resonance imaging abnormal](#), [Ovarian cancer](#), [Ovarian cyst](#), [Surgery](#)
- Write-up: Information has been received from a general practitioner concerning a 17 year old female patient with no family history of ovarian cancer who on 15-NOV-2008 and on 06-FEB-2009 was vaccinated with the first and second doses of GARDASIL (batch number, lot number not provided). The patient was not on contraceptives at time of reporting. On an unspecified date, the patient experienced significant abdominal distension. MRI was very suggestive of a malignant lesion. Ovarian cancer was consequently suspected. The patient underwent surgical operation in December 2009: genital organs were preserved and the surgeon specified that it was probably a non-malignant cyst. Anatomopathological results were awaited. The outcome was not reported at the time of reporting. The patient's ovarian cancer, abdominal distension, and ovarian cyst were considered other important medical events. Other business partner number included: E200911947. Additional information has been requested.

Overstimulation of HPV Cells in the Ovaries

Some HPV viruses are called "high-risk" types, and may cause abnormal Pap tests. They may also lead to cancer of the cervix, vulva, vagina, anus, or penis. *Centers for Disease Control and Prevention*

Since ovarian cancer is “called the silent killer” more independent studies need to be conducted on why Gardasil is stimulating HPV cells to become cancerous in other areas of the reproductive system in both women and men.

The concern is the challenge and re-challenge of the HPV vaccination series. What studies were conducted to determine that this mechanism of action may cause not only immune system overstimulation but also overstimulation of HPV if already present in the body prior to vaccination?

PCOS – Poly Cystic Ovarian Syndrome & HPV

Polycystic ovary syndrome (PCOS) is common, affecting as many as 1 out of 15 women. Often the symptoms begin in the teen years. Symptoms of PCOS are caused by changes in hormone levels. The concern is that since “estrogen dominance” due to genetic and environmental factors is increasing and that adolescent girls are producing more estrogen during menarche and that estrogen stimulates histamine production – the additional histamine present in Gardasil may be a cause of further hormone imbalance that may lead to PCOS. This overstimulation of estrogen and histamine may also be a cause of the two cases of ovarian cancer reported to VAERS.

Since menstrual cycle evaluation; i.e.; estrogen and histamine interaction/reaction – stimulation and overstimulation was not included in the clinical trials this mechanism of action affecting many of the girls adversely affected by the vaccine is of great concern.

Effect of the Menstrual Cycle and Hormonal Contraceptives on Human Papillomavirus Detection in Young, Unscreened Women

Obstetrics & Gynecology:

July 2010 - Volume 116 - Issue 1 - pp 67-75

doi: 10.1097/AOG.0b013e3181e238f0

Original Research

OBJECTIVE: To estimate the effect of the menstrual cycle and oral contraceptive pill (OCP) use on the prevalence, incidence, and persistence of human papillomavirus (HPV).

CONCLUSION: High-risk HPV detection was significantly influenced by sample timing in the menstrual cycle when analyzed separately for OCP users and women with a natural menstrual cycle. This may have implications in the future, when high-risk HPV detection may become a primary screening tool in cervical cancer prevention.

Peer Reviewed Analysis

Effect of the Menstrual Cycle and Hormonal Contraceptives on Human Papillomavirus Detection in Young Unscreened Women

The concern is that for non-contraceptive pill users HPV prevalence was higher in the follicular phase of the menstrual with estrogen dominance and histamine stimulation. What studies have been conducted on the mechanisms of action of between estrogen, histamine and HPV prevalence?

What studies have been conducted on HPV vaccines safety and efficacy if, according to CDC studies HPV viruses other than 16 & 18 are prevalent? What are the mechanisms of action between the vaccine and these other viruses? Is it known that the mechanisms of action in the vaccine do not stimulate replication of the other viruses?

Studies on the efficacy of the HPV vaccines and oral contraceptives have been studied – but not about safety; **Gardasil PPI 7.2 use with Hormonal Contraceptives, Cervarix PPI Interactions pg. 16**. Since OC's may increase the risk of cervical cancer – what is the mechanism of action between OC's and HPV vaccines and potential stimulation HPV viruses other than 16 & 18? Are studies being conducted > 5 years on the safety and efficacy of long term OC use and HPV vaccination?

Effect of the Menstrual Cycle and Hormonal Contraceptives

- ▣ VAERS ID: [325151](#)
- ▣ Vaccination Date: 2007-07-13
- ▣ Age: 20
- ▣ Submitted: 2008-09-02
- ▣ Entered: 2008-09-16
- ▣ Vaccination HEPA
- ▣ Manufacturer GLAXOSMITHKLINE BIOLOGICALS
- ▣ Vaccination HPV4
- ▣ Manufacturer MERCK & CO. INC.
- ▣ Vaccination TDAP
- ▣ Manufacturer SANOFI PASTEUR
- ▣ Other Medications: LEVOXYL .88 mcg; Birth Control
- ▣ Preexisting Conditions: Hypothyroid
- ▣ Symptoms: Death, Dyspnoea, Muscular weakness
- ▣ Write-up: April 2008, started experiencing symptoms of muscle weakness in arms and neck, they progressed to interfering with muscle weakness in throat and breathing. Patient died on August 21, 2008.

HPV Pre-testing



Dr. Sin Hang Lee F.R.C.P. (C), FCAP

Cervical-Cancer Screening – New Guidelines
and the Balance between Benefits and Harms

Need for HPV Pre-Testing

Genotype-Specific HPV Vaccines

There is no evidence that the current genotype-specific HPV vaccines are effective among the mainstream American adolescent women because the NCI does not know what “carcinogenic” HPV genotypes are prevalent in the general American female populations, which are highly heterogeneous, varying from county to county. The current HPV vaccines are shown to be effective against infection by HPV-16 and -18, and perhaps -31 and -45. The clinical trials for the currently licensed HPV vaccines, were performed in foreign, largely underdeveloped countries with high cervical cancer prevalence rates. Therefore, to rely on prophylactic vaccination using the current available HPV vaccines to prevent cervical cancer in the US is highly speculative. Three HPV studies were recently conducted in the U.S. on self-collected vaginal swabs submitted by women visiting a mobile examination center (a CDC study), 14- to 17-year-old adolescents (mostly African-American, attending a primary care clinic), and 57- to 85-year-old women. The results showed HPV-62 and HPV-84, HPV-52, and HPV-61 to be the leading genotypes. HPV-16 and HPV-18 were not the prevalent genotypes in these groups.

Need for HPV Pre-Testing

As suggested by some scientists in the field, primary HPV DNA-based screening with cytology triage and repeat HPV DNA testing of cytology-negative women appears to be the most feasible cervical screening strategy now. However, to implement such a futuristic approach requires more accurate new technologies to perform HPV DNA screening and HPV genotyping, and the effective use of the residual cytopathology human resources still available in this country. Since there is little profit in such a project, the national policy-makers do not seem to be interested in such proposals.

As to HPV vaccination, the sexually active women who decide to be vaccinated should make sure that they are not already infected by HPV-16, HPV-18, HPV-31 or HPV-45. Data from other countries proved that the vaccines are not effective if these prior infections already exist, and they may even be harmful.

Gardasil & Yeast Culture

Development of Reaction to Fungus

Reaction to Citric Acid

Commercially Prepared Citric Acid

Development of Reaction to Fungus

Fungus (yeast) exposure can evoke an aggressive TH17 immune response, and cause autoimmune symptoms to appear. Inflammatory cytokines may be produced following the activation of the TH1/TH17 immune response, producing NF-Kappa-B. The TH17/IL-23 pathway, however, increases inflammation and inhibits the body's TH1 immune response from fighting infection, *Candida albicans*, and **Aspergillus fumigatus**. The same researchers also noted a molecular connection between IL-23 and uncontrolled fungal growth. This may account for some vaccinated children presenting with increased ear-infections, and why people who receive the Gardasil vaccine (manufactured with a fungus), become highly sensitive to commercially made citric acid, that is made using the **Aspergillus fungus**. The TH17/IL-23 pathway may help contribute to the increased autoimmune prevalence in females.

Development of Reaction to Fungus

Historically, 80% of autoimmune cases occur in females, and sex hormones are known modulators of NF-Kappa-B. NF-Kappa-B can trigger the production of pro-inflammatory IL-1, IL-6, TNF- α , etc., which results in the signaling of microglia to produce inflammatory cytokines.

Reaction to Citric Acid

The primary cause is nutrient malabsorption from an inflamed or compromised GI tract, caused in most cases by acquiring a sensitivity to very small amounts of commercially made citric acid, especially those with a history of HHV-4 or when HHV-6 or the Rotavirus is present. The NO/ONOO Cycle, which mediates intracellular iron signaling in NF-Kappa-B, may also be effected, resulting in a further increase in inflammatory cytokines, due to increased NF-Kappa-B activity. With changed conditions in the body, and the immune system further compromised by decreased nutrients, together with IL-17/IL-23 causing a decreased TH-1 immune response to bacteria and fungi, dormant organisms may be signaled to replicate and become virulent. Upon replication, some of these organisms, viruses, Rotaviruses, and RETROVIRUSES, and fungi - such as Coccidioides, Aspergillus fumigatus, plus XMRV, can activate receptors, such as Toll-Like Receptor 3 (TLR3), and further intensify or prolong Hypercytokenemia. In the brain and nervous system, inflammation caused by inflammatory cytokines from microglia cells, can damage neurons.

Reaction to Citric Acid

There are also indications that heavy metals are also being freed during the rapid production of cytokines, and by the inflammation process , because high levels of heavy metals, such as aluminum, have been found in hair samples . Aluminum is a known disruptor in MS, and an adjuvant in many vaccines, including GARDASIL. Unchecked Hypercytokinemia may cause microglia to originate a massive calcium wave, resulting in a seizure.

Commercially Prepared Citric Acid

An estimated 99% of commercially prepared citric acid is made by combining corn oil with the *Aspergillus Niger* Fungus, a member of the Fungal Kingdom. The host may develop an extreme fungal sensitivity.

Various amounts of the fungal metabolites and mycotoxins of the *Aspergillus Niger* Fungus appear in commercially prepared citric acid, and contaminate many foods and prepared drinks, and medications.

These contaminants can also be found in many vitamin and mineral supplements, including some digestive enzyme supplements recommended by DAN doctors (DAN=Defeat Autism Now).

Potential Gardasil Impact on Endocrine System Functioning – Menarche to Menopause

- ▣ Irregular Cycles
- ▣ Thyroid Function
- ▣ Adrenal Fatigue
- ▣ Estrogen Dominance
- ▣ Autoimmune Disorders
 - Fibromyalgia
 - Lupus
 - Epstein Barr
 - Chronic Fatigue Syndrome
 - MS
 - Guillain-Barré Syndrome
- ▣ Glutathione Deficiency Interaction

Menarche & Irregular Cycles

Menarche occurs on average at the age of 12 – but may occur as early as age 9. Timing is influenced by *biology*, as well as *genetic* and *environmental factors*, especially *nutritional factors*. Reports of puberty and breast development as early as age 7 have also been noted.

Hormone fluctuations can begin up to two years prior to menarche. Until a rhythmic endocrine pattern is established – which may be over many years due to the above factors, this time frame has proven to be one of the most fragile in a woman's life. The introduction of medications, and vaccinations with the potential for side effects, may prove to be more risky until the endocrine system is functioning in a regular pattern. According to the NIH study on *Impact of stress, gender and menstrual cycle on immune system: possible role of nitric oxide (2001)*: “...Gender and menstrual cycle phases are other factors affecting the predisposition of individuals for certain diseases. Results from animal and human studies suggest that the distribution of immune system cells may change at different phases of the menstrual cycle.

Menarche

The lack of clinical trials of the HPV vaccines in relation to the menstrual cycle in this age group is of great concern. Then again, it is almost impossible to test since the pre-ovulatory phase is and may remain unstable for many years. Vaccinating pubescent girls at this time is like getting a shot in the dark. More and more studies are coming out on the changes in a woman's body due to hormonal shifts. The most impactful and recent study has been on changing cholesterol levels during the menstrual cycle. *Journal of Clinical Endocrinology and Metabolism.*

Menarche & HPV Studies

- According to the CDC study on the Prevalence of HPV Infection Among Females in the United States, data indicated that the burden of prevalent HPV infection among females was greater than previous estimates and was highest among those aged 20 to 24 years. However, *the prevalence of HPV vaccine types was relatively low.*
- According to the CDC ...longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women, data indicated cumulative prevalence of HPV infection in sexually active adolescent women is extremely high, *involves numerous HPV types*, and frequently results in cervical dysplasia.

Have independent studies been conducted on the safety and efficacy of the interaction of the HPV vaccine with other HPV viral strains?

Menopause

Menopause typically occurs during (although not limited to) a woman's late 40s or early 50s and is the permanent cessation of ovarian function. Hormone changes may take place 5 to 15 years prior to menopause. This transition results in a major hormonal change and includes many symptoms. The severity of those symptoms depends on the same factors associated with menarche; *biology*, as well as *genetic* and *environmental factors*, and *nutritional factors*. Menstrual irregularity may last for 1 to 3 years before menstruation ends completely.

Just as menarche is a biomarker for a woman's reproductive years, menopause becomes a biomarker for the cessation of ovulation and reproduction. Many of the same factors that occur at menarche occur with menopause; hormone imbalance and irregular menstrual patterns. Once again, medications, vaccination, become risky with hormonal shifts. One additional factor to be taken into consideration is how the reproductive years and stress have influenced a woman's overall health and well being.

Menopause

In the CDC study Prevalence of high-risk human papillomavirus among older women, in a nationally representative population, nearly 1 in 16 women aged 57-85 was found to have high-risk HPV, and prevalence was stable across older age groups.

These are high rates of numbers for an age group whose biological age may differ markedly from their chronological age.

Have independent studies been done on the 26 to 46 yr. age group under consideration for expansion of the HPV vaccine? What are the HPV viruses prevalent in this demographic? What will the interaction between the current vaccines be with other HPV strains in a body that is experiencing hormonal shifts associated with peri-menopause and menopause?

Menopause - Thyroid Function

The connection between **thyroid hormone imbalance** and menopause is often overlooked, however, over 20% of menopausal women in the U.S. are diagnosed with thyroid dysfunction. Recent studies suggest that millions more suffer from subclinical problems but are undiagnosed. For women in their late 30's or 40's, hypothyroidism is often a good indication that they are in peri-menopause.

Hypothyroidism is more common in women because hormonal imbalance acts as a trigger for thyroid problems. Peri-menopause, menopause, and pregnancy are times in a woman's life when hormonal imbalance is particularly common, and are also associated with hypothyroidism.

Menopause - Thyroid Function

Excess of estrogen, (“estrogen dominance”) combined with low Progesterone (lack of ovulation) is also a major trigger. Once again, estrogen plays a factor in hormone balance – just as in menarche. Estrogen dominance in conjunction with histamine production and the additional histamine in Gardasil and the mechanisms of action are of great concern.

Once again, the question needs to be asked – have the appropriate studies on this age group been conducted before HPV vaccine expansion into this market is approved?

Menopause - Adrenal Fatigue

Adrenal fatigue during menopause is a debilitating and complex disorder that causes body exhaustion and poor stamina. Adrenal fatigue is a result of the adrenal glands being unable to deal with anxiety and other forms of daily stress. Symptoms include:

- Excessive fatigue or exhaustion
- Not feeling rested after plenty of sleep
- Insomnia
- Inability to lose weight
- Difficult to bounce back from injury, illness, stress or exercise
- Cravings for salty and/or sweet things
- Low blood pressure
- Low libido
- Excessive thirst and urination
- Needing caffeine to get going in the morning
- Excess hunger or, on the other extreme, lack of appetite
- Irritability

Menopause - Estrogen Dominance

Estrogen dominance is a condition where a woman can have deficient, normal or excessive estrogen, but has little or no progesterone to balance its effects in the body. Even a woman with low estrogen levels can have estrogen dominance symptoms if she doesn't have any progesterone.

- ❑ Allergies, including asthma, hives, rashes, sinus congestion
- ❑ Autoimmune disorders
- ❑ Cervical dysplasia
- ❑ Depression with anxiety or agitation
- ❑ Dry eyes
- ❑ Endometrial (uterine) cancer
- ❑ Fatigue
- ❑ Foggy Thinking , Memory Loss
- ❑ Gall Bladder Disease
- ❑ Hair Loss ,
- ❑ Headaches
- ❑ Increased blood clotting (increasing risk of strokes)
- ❑ Mood swings
- ❑ Polycystic ovaries
- ❑ Sluggish metabolism
- ❑ Thyroid dysfunction mimicking hypothyroidism
- ❑ Uterine cancer
- ❑ Uterine fibroids

Only those symptoms that have the potential to be exacerbated by a vaccine adverse reaction are listed.

Menopause Autoimmune Disorders

In the past few years studies have suggested that chronic inflammation lies at the root of heart disease, cancer, osteoporosis, Alzheimer's, and autoimmune diseases like rheumatoid arthritis and psoriasis, as well as other immune disorders.

Inflammation is a particularly important issue for women in perimenopause and menopause. Studies have shown that hormone transitions in premenstrual syndrome and menopause causes inflammation and could be a key reason why women suffer 75% of all autoimmune disease.

Existing chronic inflammation in combination with the HPV vaccine that may also causes inflammation due to unknown mechanisms of action should be of great concern to not only the FDA but to physicians as well.

Menopause

Autoimmune Disorders

Adverse reactions to the HPV vaccines have for the most part been experienced by girls without pre-existing illnesses or diseases. Many of those affected have had a family history of allergies or autoimmune conditions. But other than that these girls have been high-functioning scholars and athletes.

How will the HPV vaccines affect women who have may have been previously exposed to HPV, who are prone to any of the above conditions due to hormone imbalances and a compromised immune system?

We are concerned that adequate testing on the 26 to 47 year old age group of women has not been conducted to warrant the expansion of the HPV vaccines to this market.

Glutathione Deficiency Interaction

- Athletic Girls
- Overweight Girls
- Vaccination During Paramenstrum
- Women and Aging
- Auto-immune Disease

Glutathione Deficiency - Athletes

- "We are not sure why women's testosterone elevation prior to competition is so much greater than it is in men. It is probably due to the fact that every day levels of testosterone are four times higher in men than they are in women. To effectively meet the challenge a higher production rate may be necessary," explains Dr. Alan Booth, Distinguished Professor of Sociology, Human Development and Family Studies, and Demography at Pennsylvania State University.

"Among women, pre-game testosterone increases were significantly correlated with reports of being focused just prior to the game, just as it is associated with arousal in men," Booth says.

"College Sports Scholarships," "The importance of hormones in female athletic competition,"

- James B. Adams, a professor at Arizona State University's School of Materials, ..._Adams says, elevated testosterone levels are linked to the depletion of glutathione, a substance in the body that protects it from toxic metals.

Time, "A Link Between Autism and Testosterone?" by Eben Harrell, January 15th of 2009.

Glutathione Deficiency - Athletes

- ❑ Glutathione is always in great demand and is rapidly consumed when we experience any sort of emotional or physical stress, fatigue and even moderate exercise."

Antioxidant, Blood Booster and Cell Detoxifier.

- ❑ Glutathione synthetase deficiency can be classified into three types: mild, moderate, and severe. Mild glutathione synthetase deficiency usually results in the destruction of red blood cells (hemolytic anemia)."

"...individuals affected by the severe form of this disorder may experience neurological symptoms. These problems may include seizures; a generalized slowing down of physical reactions, movements, and speech (psychomotor retardation); intellectual disability; and a loss of coordination (ataxia). Some people with severe glutathione synthetase deficiency also develop recurrent bacterial infections."

Genetics Home Reference, Glutathione synthetase deficiency, Reviewed December 2006,
<http://ghr.nlm.nih.gov/condition/glutathione-synthetase-deficiency>

Glutathione Deficiency - Overweight

- The data of the present study indicate that serum CRP as well as IL-6 circulating levels decreased during weight loss, supporting the beneficial effect of weight reduction on cardiovascular risk factor.

In our study IL-6 levels as well as isoprostane were significantly higher and glutathione peroxidase significantly lower in obese subjects compared to controls

Furthermore, IL-6 levels positively correlated with isoprostane and negatively with glutathione peroxidase in the obese, a finding which has not been previously described. After weight reduction the levels of insulin, CRP, IL-6 and isoprostane significantly decreased, whereas glutathione peroxidase significantly increased.

Plasma Interleukin-6 levels, glutathione peroxidase and isoprostane in obese women before and after weight loss. Association with cardiovascular risk factors, Maria Bougoulia, Athanassios Triantos, George Koliakos, Biochemistry Department, Aristotele University Medical School, Thessaloniki, Greece http://www.hormones.gr/preview.php?c_id=153

- Regional fat distribution (RFD) has been associated with metabolic derangements in populations with obesity. For example, upper body fat patterning is associated with higher levels of free testosterone (FT) ..."

[Int J Sport Nutr Exerc Metab.](#) 2001 Dec;11(4):451-65.,

Glutathione Deficiency - Overweight

- "Compared with normal-weight children of the same age, gender, and pubertal stage, obese prepubertal children and obese pubertal girls demonstrated significantly increased testosterone..."

"The decrease of testosterone serum levels after weight loss in prepubertal children and pubertal girls points to a reversible increase of testosterone in obesity. This change in testosterone serum levels is not caused by other influencing factors because, in a collective of obese prepubertal children and obese girls of similar age, gender, and degree of overweight without weight loss, there were no changes in testosterone concentrations over the same time period, whereas in the group of obese pubertal girls without weight loss, testosterone levels increased.

Journal of Clinical Endocrinology & Metabolism , doi:10.1210/jc.2005-0438, [The Journal of Clinical Endocrinology & Metabolism](#) Vol. 90, No. 10 5588-5595 Copyright © 2005 by The Endocrine Society

- "Glutathione peroxidase was significantly lower in the obese women than in the controls."

"The mean weight, BMI, W/H ratio, waist circumference, %, body fat, cholesterol, triglycerides, CRP, insulin, HOMA-IR, interleukin-6 and isoprostane were significantly reduced after weight loss ($p < 0.001$), whereas glutathione peroxidase was significantly increased after weight reduction ($p < 0.001$)."

The full report, ["Pathogenesis of polycystic ovary syndrome: What is the role of obesity?"](#) appears in *Metabolism* (2004;53:358-376).

Glutathione Deficiency During Paramenstrum

Estrogens, like vitamin E ... The positive relationship between E2 plasma levels and GSH-Px erythrocyte activity during the menstrual cycle further supports the hypothesis that the antioxidant activity of estrogens may also be a consequence of a modulation of GSH-Px enzyme activity by an increase in the GSH-Px transcription (Massafra *et al.* 1997).

“Our results document a rise in GSH-Px activity during the menstrual cycle, which is particularly evident from the late follicular to the early luteal phase, a period in which there is the maximum ovarian production of estrogen.”

Effects of estrogens and androgens on erythrocyte antioxidant superoxide dismutase, catalase and glutathione peroxidase activities during the menstrual cycle. [*Journal of Endocrinology* \(2000\) 167, 447-452](#)

Glutathione Deficiency Women and Aging

- In contrast, Julius et al ([41](#)) observed a positive correlation of glutathione with age ($n = 33$; $P < 0.01$). Lastly, Richie et al ([42](#)) also observed lower glutathione concentrations in subjects aged >55 y than in younger subjects, but the difference was significant only in women ($n = 231$; $P < 0.01$).

([41](#)) Julius M, Lang CA, Gleiberman L, Harburg E, DiFranceisco W, Schork A. Glutathione and morbidity in a community-based sample of elderly. *J Clin Epidemiol* 1994;47:1021-6. [[Medline](#)]

([42](#)) Richie JP, Skowronski L, Abraham P, Leutzinger Y. Blood glutathione concentrations in a large-scale human study. *Clin Chem* 1996;42:64-70. [[Abstract/Free Full Text](#)]

American Journal of Clinical Nutrition, Vol. 71, No. 5, 1194-1200, May 2000, © 2000 [American Society for Clinical Nutrition](#), Direct correlation of glutathione and ascorbate and their dependence on age and season in human lymphocytes

- GSH content was similar in males and females and decreased with age in both sexes. Since GSH is correlated with protection against cellular or cytogenetic damage, reduction of GSH content during aging may be a factor of relevance for the increased risk of developing diseases such as cancer at an older age.

Carcinogenesis, vol.19 no.10 pp. 1873-1875, 1998. [Age and gender dependent levels of glutathione and glutathione S-transferases in human lymphocytes.](#)

Glutathione Deficiency Women and Aging

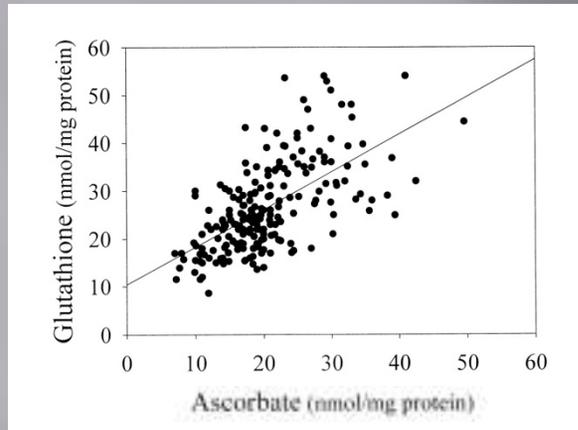


FIGURE 1. . Correlation of ascorbate and glutathione concentrations in human lymphocytes. The following linear function was fitted to the data: $y = 10.4 + 0.78x$ ($r = 0.62$, $P < 0.001$; $n = 240$) where x and y are the intracellular concentrations of ascorbate and glutathione, respectively, in human lymphocytes. The compounds were normalized to total protein as measured by the Bradford assay.

Although there is a trend toward lower glutathione values in elderly than in young or middle-aged individuals, there have been contradictions. Lang et al ([40](#)) reported a 17% lower glutathione concentration in whole blood in the elderly (60–79 y; $n = 60$) than in the young (20–39 y; $n = 40$) ($P < 0.001$). In contrast, Julius et al ([41](#)) observed a positive correlation of glutathione with age ($n = 33$; $P < 0.01$). Lastly, Richie et al ([42](#)) also observed lower glutathione concentrations in subjects aged >55 y than in younger subjects, but the difference was significant only in women ($n = 231$; $P < 0.01$).

[Direct correlation of glutathione and ascorbate and their dependence on age and season in human lymphocytes](#), American Journal of Clinical Nutrition, Vol. 71, No. 5, 1194-1200, May 2000

Glutathione Deficiency Auto-Immune Disease

- ALS - “Furthermore, depletion of GSH decreased mitochondrial function, facilitated apoptosis inducing factor (AIF) translocation, ...and consequently led to motor neuron-like cell apoptosis.”

“Taken together, the in vitro and in vivo data presented in the current report demonstrated that decreased GSH promotes multiple apoptotic pathways contributing, at least partially, to motor neuron degeneration in ALS.”

Neuroscience (2007), Depletion of reduced glutathione enhances motor neuron degeneration in vitro and in vivo. L Chi, Y Ke, C Luo, D Gozal, R Liu,

- MS - “Oxidative stress has been implicated in inflammatory demyelination. The glutathione S-transferase (GST) supergene family encodes isoenzymes that appear to be critical in protection against oxidative stress.”

“Our results suggest that long-term prognosis in MS is influenced by a genetically determined ability to remove the toxic products of oxidative stress.”

Glutathione S-transferase polymorphisms in MS, *Neurology* 2000;54:552, © 2000 American Academy of Neurology

Glutathione Deficiency Auto-Immune Disease

- ▣ ME/CFS/CFIDS - Since the immune system of the afflicted individual is hyperactive, the body's store of glutathione is soon depleted. This substance is required to support the tremendous proliferation of both the T and B lymphocytes during a full immune response, because these cells use free radicals (very unstable molecules) in the battle against microbial pathogens. These free radicals cause damage to body tissues as well as the invading pathogens, unless there are sufficient antioxidant substances and enzymes present to deactivate these unstable molecules released during the immune response.

Dr. Paul Cheney: *Evidence for Glutathione Deficiency in CFS*. Paper delivered at the Third Annual Congress of BioEnergetic Medicine held in Orlando, Florida, Feb 5-7, 1999

Mechanisms of IgE-mediated Allergy & Non-IgE-mediated Immune Reactions

Expert Rev Clin Immunol. 2010;6(3):397-411. © 2010 Expert Reviews Ltd.

- IgE-mediated allergic diseases (e.g., allergic rhinoconjunctivitis, atopic asthma and food allergy) are prevalent (up to 30%) in the general population and are increasing in developed countries.
- ... exposure to even minute amounts of allergen results in a cross-linking of IgE Abs on the cell surface of effector cells.^[23] This results in activation of the FcεRI-expressing effector cells (mast cells and basophils), causing the release of various mediators, including histamine, leukotrienes and interleukins within minutes of allergen exposure.^[41]
- It is believed that Th2-mediated immune defense developed against large extracellular organisms, such as helminths, and that IgE is a key factor in such a mechanism.
- By contrast, allergen-induced Th2 responses lack such suppressive components, leading to uncontrolled inflammatory responses. In other words, allergic diseases may be regarded as the result of ill-adapted Th2 responses.

Mechanisms of IgE-mediated Allergy & Non-IgE-mediated Immune Reactions

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▣ Non-IgE-mediated Immune Diseases (Conditions) Associated with Respiratory & GI Symptoms

- **Non-allergic Rhinitis** - Rhinitis is a common condition affecting up to 25% of the general population
- **Non-atopic Asthma** - Nonatopic (intrinsic) asthma is defined as asthma in the absence of allergen-specific IgE antibodies and accounts for approximately 20% of the asthma population.
- **Rhinosinusitis/Otitis Media** - Sinusitis and otitis media (OM) often cause significant respiratory symptoms.
- **Celiac Disease** - Celiac disease (CD) is now considered to be an immune-mediated enteropathy caused by wheat protein ingestion in susceptible individuals,
- **Non-IgE-mediated Food Allergy** - In contrast to IgE-mediated FA, NFA symptoms typically occur hours after exposure, rendering it difficult to appreciate a causal relationship between exposure to the offending food and resulting clinical symptoms.

Mechanisms of IgE-mediated Allergy & Non-IgE-mediated Immune Reactions

Expert Rev Clin Immunol. 2010;6(3):397-411. © 2010 Expert Reviews Ltd.

- ▣ Possible Effects of Allergic & Non-allergic Disorders on Cognition & Behavioral Symptoms
 - ▣ Neuropsychiatric Effects of Allergic & Non-allergic Diseases in the General Population
 - ▣ Allergic Rhinitis
 - ▣ Asthma
 - ▣ GI Disorders
 - ▣ Celiac Disease
 - ▣ Non-IgE-mediated FA (Food Allergy)

Orthostatic Hypotension Cause of Death in HPV Vaccine Victims?

Orthostatic intolerance affects an estimated 500,000 Americans and causes a wide range of disabilities. *It is a disorder that more frequently affects young women (female-to-male ratio at least 4:1), often less than 35 years of age.* Most of these patients experience an excessive heart rate increase when they stand. This heart rate increase is a sign that the cardiovascular system is working hard to maintain blood pressure and blood flow to the brain in the presence of a disordered cardiovascular regulation. Other than essential hypertension, OI is the most common disorder of blood pressure regulation. OI is also the most frequently encountered dysautonomia, accounting for the bulk of patients referred to centers specializing in autonomic disorders.

[Vanderbilt Autonomic Dysfunction Center](#)

[155 Events Where Blood Pressure is Decreased Post HPV Vaccination](#)

Development of New Medications for Vaccine Adverse Reactions

Merck

<http://www.merck.com/research/pipeline/home.html?WT.svl=content>

GlaxoSmithKline

http://www.gsk.com/investors/product_pipeline/docs/GSK-product-pipeline-Feb-2010.pdf

Development of New Medications Merck

PHASE II

Allergy, Immunotherapy, SCH
900237

Asthma, MK 0476C

Hot Flashes,
MK-3613

Atrial Fibrillation, vernakalant
(MK-6621[oral])

Insomnia,
MK-6096

Trombosis, betrixaban
(MK-4448)

PHASE III

Diabetes,
sitagliptin/pioglitazone
(MK-0431C)

Fertility, corifollitropin alfa
injection
(SCH 900962)

Insomnia,
MK-4305

Migraine, telcagepant
(MK-0974)

Neuromuscular Blockade
Reversal, BRIDION
(SCH 900616)(US)

Trombosis, vorapaxar
(SCH 530348)

UNDER REVIEW

Asthma, DULERA
(SCH 418131)(US/EU)

Atrial Fibrillation
BRINAVESS
(MK-6621)(EU)

Schizophrenia, Bipolar Disorder
SYCREST
(SCH 900274)(EU)

Development of New Medications GlaxoSmithKline

Therapeutic Area	Compound / Vaccine	Indication	Phase
Biopharmaceuticals	1070806	metabolic disease	I
	1223249	amyotrophic lateral sclerosis	I
	APN01	acute respiratory distress syndrome	I
	iboctadekin† (+ Doxil)	ovarian cancer	I
	iboctadekin† (+ rituximab)	follicular lymphoma	I
	otelixizumab	type 1 diabetes	I
	315234	rheumatoid arthritis	II
	Arzerra (ofatumumab)†	follicular lymphoma (relapsed patients)	II
	Benlysta (belimumab)†	systemic lupus erythematosus	II
	ofatumumab†	multiple sclerosis	II
	Benlysta (belimumab)†	systemic lupus erythematosus	III
	ofatumumab†	rheumatoid arthritis	III
	otelixizumab†	type 1 diabetes	III
Syncria†	type 2 diabetes	III	

Development of New Medications GlaxoSmithKline

Therapeutic Area	Compound / Vaccine	Indication	Phase
Neurosciences	586529	depression & anxiety	I
	618334	drug dependency	I
	163090	depression & anxiety	II
	561679†	depression & anxiety	II
	649868†	sleep disorders	II
	2402968 (PRO051)†	Duchenne muscular dystrophy	II
	firategrast†	multiple sclerosis	II
	Horizant (1838262)†	migraine prophylaxis	II
	Horizant (1838262)†	neuropathic pain	II
	losmapimod	pain (also cardiovascular disease, COPD & depression)	II
	losmapimod	depression (also cardioscular disease, COPD & pain)	II
	almorexant†	insomnia	III
	Horizant (1838262)†	restless legs syndrome	Submitted
	retigabine†	epilepsy - partial seizures	Submitted

Conclusion

Do No Harm

Considering the evidence presented in the March, 2010 FDA “Listening Session” presentation in combination with the peer-reviewed studies and research presented in this presentation, it proves beyond a shadow of a doubt that the protocol for the HPV vaccines and the challenge re-challenge is a potential mechanism of action in the increasing reports of adverse events.

We have also demonstrated that a woman’s age – whether she is in menarche, early adolescence or in menopause needs to be taken into consideration for any and all medical procedures or drug regimes. To not do so is to ignore the neural endocrine influence on a woman’s health and well being.

Conclusion

Do No Harm

We have shown that pre-existing allergies, elevated IgE levels, exercise regimen, auto-immune functions, fungus used in HPV vaccine production, besides a variety of other conditions potentially cause an adverse reaction to this vaccine. We know that allergies now affect at least 33% of the population and we have seen that non-allergic study subjects 73.3% have a new medical condition. This data must be analyzed carefully.

For what purpose does a clinical trial on a healthy demographic serve? In our humble opinion it is only a ruse for passage of a drug that may cause irreparable harm.

We have proven beyond a shadow of a doubt that the HPV vaccines can and do cause harm to immune functioning, especially with glutathione depletion.

Conclusion

Do No Harm

In a recently released study [Enhanced neuronal expression of major histocompatibility complex class I leads to aberrations in neurodevelopment and neurorepair](#) from the Department of Molecular and Medical Pharmacology, University of California, Los Angeles, it was noted that:

When neurons sense infection or damage to the brain, they produce more MHC major histocompatibility complex),” said Daniel Kaufman, professor of molecular and medical pharmacology at the David Geffen School of Medicine at UCLA. Increased levels of MHC affect how the brain develops in pregnant mice and may explain schizophrenia, autism and other neurological disorders in offspring.

[Immune Response Offers Possible Insight to Schizophrenia, Autism](#)
Psych Central, 10.20.10

Conclusion

Do No Harm

According to [Wikipedia](#):

Because MHC genes must defend against a great diversity of microbes in the environment, with a great diversity of proteins, the MHC genes themselves must be diverse. The MHC is the most gene-dense region of the mammalian genome. MHC genes vary greatly from individual to individual, that is, MHC alleles have polymorphisms (diversity). This polymorphism is adaptive in evolution because it increases the likelihood that at least some individuals of a population will survive an epidemic.^[2]

Conclusion

Do No Harm

To conclude:

1. We are now aware that HPV does not cause cervical cancer [Cervical Cancer Prevention, Health Professional Version](#), published by the National Cancer Institute (NCI):

The finding of HPV viral DNA integrated in most cellular genomes of cervical carcinomas supports epidemiologic data linking this agent to cervical cancer however, direct causation has not been demonstrated.

2. In addition research shows that Amphiregulin stimulates HPV immortalized cervical cells and is the cause of cervical cancer cell growth. [Amphiregulin as an important autocrine factor that mediates growth stimulation of HPV-immortalized cervical cells by IL-1a or TNF-a.](#)

Conclusion

Do No Harm

3. HPV 16 & 18 may not be the prevalent strains found in the U.S. population – [Consumer Engaged Prevention of Cervical Cancer](#)

The current type-specific HPV vaccines have been claimed to be almost 100% effective against infection by HPV-16 and HPV-18, and perhaps also against HPV-31 and HPV-45 infections. However, we do not know if these four HPV types are the most prevalent carcinogenic HPV genotypes in the U.S. According to two published reports [2, 3] - one by the CDC, HPV-52 not HPV-16 or HPV-18 was found to be the most prevalent “carcinogenic” genotype infecting young American women.

Sin Hang Lee, MD
Pathologist, Milford Hospital and Director,
Milford Medical Laboratory, Milford, CT

Conclusion

Do No Harm

If this protocol continues the FDA, CDC, Merck and GlaxoSmithKline will have put a generation of adolescent girls and potentially older women at risk for developing a new medical condition and/or autoimmune diseases from a vaccine designed to target viral strains that may not be prevalent in the majority of the population – and for a virus whose direct causation to cervical cancer has not been demonstrated.

10.20.10 HPV Vaccine VAERS Data

Adverse Reactions

HPV and HPV4	19618
HPV 2	483
Total	20101

Deaths

HPV and HPV4	80
HPV2	4
Total	84