

# Human Papilloma Virus (HPV) Infection And Their Connection To Cancer Of The Neck Of The Uterus, Vagina, Vulva And Rectum”

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Note: for the latest updates, read the section “Recent News on the HPV Vaccine” at the end of this document.

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## **PART ONE OF SIX: HUMAN PAPILOMA VIRUSES**

The term Human Papilloma Virus (HPV) applies to all the members of a family of virus like a family name would. More than 105 different HPV “types” have been isolated so far. Each type is like one of the siblings: in certain ways similar and yet each one very different. In laboratory work, each type is identified by its specific DNA (genetic material) and given a number that is the equivalent of a first name: when we write HPV 12 and HPV 8, it is the same as writing Fox, Mary and Fox, Joseph.

For practical purposes we divide the siblings of the HPV family into “good ones” and “bad ones”. The good ones (Low Risk Types: LRT) have not been associated with the formation of cancer, the bad ones (High Risk Types: HRT) have.

On laboratory reports, several HPV types are grouped together as HRT and others as LRT. The report would read: “The sample is positive for one or more of the following HRT-HPV: 16,18,31,33,35,39,45,51,52,56,58,59,68, and 82.”

In everyday practice it would be too expensive to test each individual type, and the identification of any member of a group provides sufficient information to guide our clinical decision making.

All the HPV viruses live exclusively in the superficial tissue that covers our body parts: the skin, the lining of genital organs, urethra and bladder, rectum, vocal cords, and esophagus. HPV do not enter into the blood stream and do not infect the organs underneath their cover-sheath called *epithelium* (= cover of the tender and nourishing tissue). There is no documentation that HPV can infect internal organs or the nervous system.

### **What can HPV do to us?**

The LRT are responsible for the formation of verruca, papilloma and venereal warts: all benign diseases. They do not induce cancer.

The HRT can, over many years, induce tissue changes that will lead to the formation of cancer of the epithelium. It is very important to understand that the changes induced by HRT-HPV remain superficial for many years, confined within the epithelium. In this “intra-epithelial” stage we can always treat them, preventing the spread to deeper tissue that coincides with the development of cancer. More so, in the intra-epithelial stage the immune system can act on the lesion very efficiently, blocking its progression and completely eliminating it, even if the virus is still present.

The *carcinogenic* (cancer inducing) property of HRT-HPV is much more dangerous for women than for men. Women, for reasons that we do not understand, are prone to this complication that is only the exception in men.

### **Can we get rid of HPV infections?**

Probably not. With the tools that we have now we can only identify the presence of HPV, monitor it, and help the immune system fight virus and virus related lesions. We do not have yet the ability to permanently eliminate the virus from our bodies. Even surgically removing lesions is just a “help to the immune system” that has to fight a smaller number of viral units and can better keep them at bay. Removing the lesions does not completely eliminate the virus.

### **What does it mean that the HPV test is negative?**

When we test for the presence of HPV we use laboratory tools that have limits. Below a certain number of viral units we cannot detect viral presence any more: a “negative” report does not guarantee that there is no virus, but that there is very little of it, if any.

**At this point I always hear the question: “Who gave me this infection?”**

This is a question that has no clear answer.

We cannot be sure of the time or the way of transmission. We do know that HPV can be transmitted at birth, from mother to child, and that we can easily transfer these viruses with every kind of intimate contact so common among toddlers. So, at the time of first intercourse, each partner brings to the other her/his own collection of HPV to share. Sexual intercourse, in every form, is a very effective method of transmission, but not the first or the only one.

**The other question that I hear often is: “How do we figure out that we have an HPV infection?”**

We do it in three ways: 1) if we recognize papillomas, or venereal warts; 2) if the pap smear is abnormal and the abnormality is further confirmed by other tests; and 3) if the test for HPV DNA is positive.

There are no symptoms that we can go by to know if we are developing lesions; there are no time markers to understand if the lesion is due to a recent contact or to a breach of the immune system allowing an old infection to act up. One can have a positive test for HRT-HPV and have no lesions at all, for a long time or forever. It is also possible, but very infrequent, to have advanced lesions and to test negative at the HPV test.

**What do we know of the interaction between HPV and our bodies?**

- ❖ We know that both HPV lesions and laboratory-detected HPV activity can disappear and reappear over time.
- ❖ We know that the first identified HPV lesion/activity in a teenager is often transitory: in 50% of cases the immune system will be able to control the virus eliminating the lesion in the following one to two years.
- ❖ We know that the same is true for a 30 year-old woman who has just become sexually active for the first time: a newly acquired infection has 50% chances to be successfully controlled by an intact immune system, within a couple of years.
- ❖ We know that lesion/activity can recur/reactivate even after many years of celibacy and negative testing.
- ❖ We know that when our immune system is weakened (HIV+, pregnancy, chemotherapy, long-term steroid treatment, old age, excessive stress, depression, sleep deprivation...) the HPV activity tends to remain positive and the HPV-related lesions tend to worsen.
- ❖ We know that HPV is transmissible during labor, and later during toddler-playing.
- ❖ We know that each new sexual partner might bring new HPV types, starting a new cycle of infection.
- ❖ We know that condoms do not prevent transmission, because the virus is all over the skin and not only in the ejaculate.
- ❖ We know that digital as well as oral sex can transmit infection.
- ❖ We know that anal lesions increase the risk of cancer of the rectum, both in men and women.
- ❖ We know that men are a reservoir of HPV, not unlike women, but testing and treatment for them is still controversial.
- ❖ We know that we have to learn much more about HPV....

**What about a vaccine?**

- ❖ A vaccine against the most virulent HRT HPV is ready for human use.
- ❖ To prevent infections, the vaccine will have to be administered before starting sexual activity, or even at a much earlier age. Eventually we might have a population

completely vaccinated...but it will take a long time. In the meanwhile, we need other strategies to avoid HPV related complications.

## **PART TWO OF SIX: THE NATURAL HISTORY OF HPV-RELATED LESIONS, AND AN EXPLANATION OF THE DIFFICULT WORDS USED IN THEIR SCIENTIFIC CLASSIFICATION**

We have seen that HPV viruses live only in the epithelium, and that the interaction between virus and immune system determines the future of the infection. In 50% of cases, within 24 months, the viral load is reduced to the point of not being detectable: in absence of other infections, these women are at very low risk of developing lesions.

Those who remain positive might owe this to new infections (new partners), to inadequate immune system activity, or to both these reasons. No matter what the cause, the risk of intra-epithelial lesions increases, but only a minority of women will develop persistent and progressive ones.

The progression from persistent intra-epithelial lesion to cancer takes approximately 10 years. This long span of time gives us the opportunity to screen women and intervene with effective treatment before the development of cancer.

Impaired immune system function (HIV infection, long-term steroid use, chemotherapy, radiotherapy, etc.) facilitates the progression from precancerous lesion to cancer: in these cases instead of several years, we sometimes see substantial progression over several months.

For anatomical and physiological reasons that are beyond the scope of this article, the large majority of pre-cancerous lesions develop on the intra-vaginal portion of the neck of the uterus that is covered by squamous epithelium. A minority of lesions can develop in the vagina, on the vulva, the perineum, rectum and, exceptionally, vocal cords: all organs covered by squamous epithelium (similar to the skin). HPV's have a marked propensity toward infecting squamous epithelium; occasionally they will also infect glandular epithelium (inner part of the uterus, Bartholin glands, etc.).

From a population point of view, the most important pre-cancerous lesions are the most frequently encountered: these are the cervical ones, both squamous and glandular. In absence of screening, cervical cancer would be the most frequent genital cancer in women, while vaginal cancer would account for only 1% . Vulvar cancer is rare and not amenable to pap-smear screening. Anal and rectal cancer are also very rare in those who do not practice anal sex; for those who do it is prudent to use pap-smear and HPV detection. The cancer of vocal cords is very rare and not subject to screening at all.

From the point of view of the individual, the only important lesion is her or his, no matter how irrelevant for statisticians and epidemiologists!

Reflecting the evolution of our understanding of the natural history of epithelial cancer formation, the scientific terminology has changed several times, since the introduction of the pap-smear in the 30's, The link between HRT-HPV and epithelial carcinogenesis was first identified in the 70's.

Here is a simplified guide through the labyrinth of present medical terminology:

First of all we need to make clear that we have two sets of terminologies: one used for screening and the other for final diagnosis. Screening and final diagnosis are two different concepts. Screening aims at identifying people that are at risk for a certain disease. Final diagnosis firmly identifies the disease itself. The screening suggests, but only through the clinical work-up process we reach a firm, final opinion: the diagnosis.

Let us start with the diagnosis. This is based on tissue samples called biopsies that allow pathologists to see the epithelium and the underlying tissue structure, as we see the layers of a cake when we slice it. Let us concentrate on the cervix only: if the lesion is limited to the epithelium it is called Cervical Intra-epithelial Neoplasia (CIN). Neoplasia (*neo* = new, and *plasis* = formation) describes a new set of cells altering the normal epithelia architecture.

Depending on the degree of epithelial architectural alteration, the CIN is subdivided in three “grades” of severity: 1 for the mildest, 2 for the intermediate, and 3 for the most severe.

The term “dysplasia” (*dys* = abnormal, and *plasis* = formation) was once utilized instead of the more specific one: intra-epithelial neoplasia.

When the neoplasia is no longer limited to the epithelium, but starts extending into the underlying tissues, we describe it as Invasive Cervical Cancer, but we still distinguish between very shallow (micro-invasion) and more advanced penetration (frank-invasion). In assessing the spread of cancer we use the term “stage”, not “grade”.

“Grade” and “stage” are not interchangeable terminology, unless we like to end up with great confusion between pre-cancerous lesions and cancer.

Let us now consider the terminology of screening, which is the terminology of pap-test. The pap-test examines the appearance of superficial, desquamated cells, not the structure of tissue. Errors might derive from inadequate sampling (too little material, not the right site, blood and inflammatory material obscuring the epithelial cells), from artifacts due to atrophy of the epithelium (changes due to postmenopausal lack of sex hormones, lactation, and radiation) or to inadequate preservation.

The abnormality most frequently identified by pap-test is described as Atypical Squamous Cells (ASC). An individual woman with ASC has approximately 17% chances of having a diagnosis of CIN 2 or 3, and one in a thousand to have cancer.

Low Grade Squamous Intra-epithelial Lesion (LG-SIL) suggests the presence of CIN 1, while High Grade Squamous Intra-epithelial Lesion (HG-SIL) suggests CIN 2-3. Suspected Carcinoma is a clear statement that does not require explanation. The chance of harboring a CIN 2-3, or cancer increases with the degree of abnormality detected by the pap-test

Occasionally, the pap-test report mentions the presence of Normal Glandular Cells or Abnormal Glandular Cells. Lesions of the glandular epithelium are rare and can be differentiated by pap-test because glandular and squamous cells do not look alike. The glandular cells might come from the lining of the inner part of the uterus or from abnormal areas of the vagina.

Now that we understand the meaning of screening and diagnostic vocabulary, we are ready to talk about the screening and diagnostic process itself.

## **PART THREE OF SIX: SCREENING VS. MANAGEMENT OF HPV-POSITIVE CASES**

### **What does “testing” mean?**

When we speak about testing for HPV-related diseases we actually mean two different things: “screening”, and “positive-case management”

### **Screening.**

*A screening test is used to separate from a large group of apparently well persons those who have a high probability of having the disease under study, so that they may be given a diagnostic work-up and, if diseased, brought to treatment.*

Individuals affected by HPV-related disease are symptom-less most of the time: they would not seek medical attention because they feel well. This is why screening is done periodically for individuals that are at risk.

High risk types HPV positivity and/or abnormal pap-smear are both considered positive screening tests: they are only suggestive, not diagnostic of HPV-related disease.

### **Positive-case management**

A positive screening test needs to be confirmed by more specific, complementary tests to determine who needs treatment and who does not. The work-up as well as the treatment are influenced by the individual’s needs/preference as well as the physician’s training /equipment.

### **Can we eliminate HPV infection and HPV-related disease by screening?**

In view of what we said about HPV transmission, it is clear that it will not be possible to avoid it, until we will have the entire population successfully vaccinated before toddler time. As things are now, our only realistic screening aim is to detect precancerous (intra-epithelial) lesions in women and treat them before they progress to cancer (spreading beyond the epithelium). Therefore we concentrate on screening the age groups most at risk for intra-epithelial lesions.

### **Who is at risk for HRT-HPV?**

Every individual who is sexually active. The risk increases with the length of sexual activity and the number of sex-partners. The risk is also higher in individuals with an impaired immune system.

### **Does a positive HPV test mean that one has HPV-induced neoplasia?**

No, it does not. Most of the times HPV infection is kept at bay by our immune system and, over time, even HPV testing becomes negative (because too little virus is shed for identification to be positive). If a person with an intact immune system remains HPV positive for more than two years the chance to have HPV-induced neoplasia increases, and further work-up is warranted. Repeated HPV testing in individuals with impaired immune systems is not useful, because the test tends to remain positive all the time: in these groups pap smear is more important.

### **Who is at risk for HPV-induced neoplasia ?**

Low-grade neoplasia (CIN 1, VAIN 1, VIN 1) is very common among sexually active teenage women, but this mild abnormality does not require treatment, only long-term monitoring. High-grade neoplasia is very rarely encountered in women younger than 25-30 years of age.

### **Why are men not screened?**

At the present time, screening is restricted to women. This makes sense only if we consider that extending screening to the male population, in absence of an effective treatment for men, is not a realistic method of containment for HPV infection.

The decision to screen women is based on the fact that their risk of developing HPV-induced cancer is much higher than men, and that both cost-effective testing and treatment methods, for women, are available.

### **Testing When?**

In a society where the majority of individuals become sexually active in their teens, and with multiple partners, teenage women become HPV-test positive within months from initiation of sexual activity and they might even develop low-grade CIN. We know that 50% of these early sex-related infections and mild lesions will be controlled by the immune system over the following two years. We also know that those women who remain positive after two years are at risk to develop high-grade CIN, and progression to cancer. Therefore it is cost-effective to start screening two to three years after the beginning of sexual activity to identify young women at risk of HPV-induced neoplasia.

The interval and manner of subsequent testing will be determined by the result of the first pap-test, the individual's life-style (number of partners, tobacco smoking, etc.), and by the presence of immune compromising therapies or conditions (HIV, chemotherapy, long-term steroid therapy, radiation, etc).

### **Testing how?**

The tests utilized to detect HPV-related lesions are pap-smear, HRT-HPV identification, colposcopy and evaluation of biopsies. We will talk of each one to understand its role.

## **PART FOUR OF SIX: TESTING OPTIONS**

### **PAP-SMEAR.**

The pap-smear was introduced more than 60 years ago by Dr. Papanicolaou, to detect cancer of the cervix before it became clinically obvious and very difficult to treat. It was soon adopted as annual screening because it was reliable, simple and inexpensive. Before the screening era, cancer of the cervix was the most common genital cancer in sexually active women. In the industrialized nations, where adequate treatment for early cancer is available, the pap-smear saved and continues to save millions of women's lives. Nowadays, in the underdeveloped nations screening has not been adopted because treatment is not available.

The pap-smear is a painless procedure easily performed during a vaginal exam, by scraping the surface of the cervix and vagina to obtain a sample of desquamating cells that are afterwards analyzed.

#### **The technicalities of pap-smear.**

It is obvious that the report of a pap-smear depends heavily on sampling technique, cells and preservation variables. This test is successful because it is easy to master how to perform it, with little training. The laboratory interpretation is more complex and a reputable laboratory should have well trained technicians and pathologists, should not overwork them (more mistakes), and should follow clear and up-dated interpretation guidelines.

Here are two suggestions that you can follow to avoid lab errors: have your pap taken far from menstruation, because blood and inflammatory cells can make reading difficult; wait at least 8 weeks after a delivery, miscarriage, or abortion to allow the uterus to clear completely all remnants of pregnancy cells that could look like cancer cells.

#### **Side benefits of the pap-smear**

Side benefits of a pap-smear are the sporadic detection of a few other infections that require treatment: yeast, trichomonas vaginitis, and bacterial vaginosis. These infections can be missed by the pap-smear because it is not the test of choice to diagnose them.

#### **HPV identification test.**

The HPV-identification test has been introduced only recently and accepted by several nations as integral part of their screening policy due to its favorable cost-effective analysis in certain segments of the population.

Only the isolation of members of the HRT-HPV group is important for the identification of precancerous lesions and cancer.

It is recommended to avoid HRT-HPV testing for women under 30 years of age, unless their pap-test is positive for unclear lesions (ASC-US = abnormal squamous cells of undetermined significance). A positive HRT-HPV in these cases will warrant further work-up. A negative HRT-HPV would leave open the choice between immediate further work-up or repeated HPV-pap at short interval.

As we have seen, the majority of sexually active teens would be HRT-HPV positive due to their newly acquired infections destined to be self-limited within a couple of years in 50% of cases: HPV testing in this segment of the population would only scare many people unnecessarily and result in too many unnecessary and costly work-ups. Therefore, up to 30 years of age, we screen exclusively with pap-smear, adding HRT-HPV testing only as stated above.

### **What is the advantage of combining HRT-HPV and pap-test at age 30 and above?**

As the progression from persistent HRT-HPV infections to neoplasia is very slow, CIN 2-3 lesions start to be more prevalent 10 years after the initiation of sexual activity. Cervical cancer is very rare before the age of 25-30, and its prevalence progressively increases reaching its peak in the late 30's.

Studies have demonstrated both immediate and prospective advantages of combined testing in this age group. Women negative for the combined test have less than 1% risk of harboring a high-grade lesion (CIN 2-3 or cancer). Furthermore, the risk of developing CIN 2-3 within three to five years from a negative combined test is less than one in 400, while the risk is 4.5% if either the HRT-HPV or the pap-test is positive, even when immediate work-up by colposcopy does not identify any concurrent lesion.

In other words, a negative pap+HPV at 30 years of age increases our confidence that no important lesion is and will be present for at least three years, therefore cutting down costs, because screening need be repeated not in one, but only in three years.

The two tests can be done at the same time, with the same sampling tools, and their performance requires only basic training sheared by medical and paramedical personnel.

### **COLPOSCOPY**

colposcopy (*colpos* = vagina, *scopo* = to examine) is an endoscopy (*endo* = *internal*) that requires specialized training and is more expensive and time consuming than a screening test. In the interest of cost-effectiveness it is now favored to follow an ASC pap-test with HRT-HPV, reserving colposcopy only for the HRT-HPV positive cases. Colposcopy is always indicated for pap-smear reading higher than ASC (i.e.: LG-SIL, HG-SIL, and suspected cancer).

The colposcope is a glorified microscope that remains outside of your body and allows the examiner to inspect the tissue surface identifying lesions not visible with the naked eye. Experienced colposcopists should know how to make this examination very tolerable and thorough, they also should be able to identify the area where the lesion is most advanced, and to take representative biopsies.

Colposcopy is complementary to the screening tests, because it can give information about the extension of disease, its location, and accessibility for treatment. In other words: colposcopy allows us to map the areas of disease, to evaluate the degree of neoplasia and to chose the most advanced areas for target biopsy.

*Colposcopy is considered adequate only when the entire areas of disease can be explored. When this is not possible, the colposcopy is considered non-conclusive, a fact that should be clearly stated on the report. A colposcopy report should always state if the entire junctional area between the internal and the external cervical linings was visible. When it is not visible, part of the lesions can be missed, and often these are the most advanced ones.*

### **Colposcopy in special conditions**

Colposcopy can be done at any age, but during menstruation it is impossible to examine the vagina and the neck of the uterus correctly, due to the presence of blood.

Lack of sexual hormones might make the vagina very thin and inelastic, causing discomfort and bleeding that can be avoided by using very small quantities of hormones, directly applied to the vagina, for two weeks prior to the examination.

When the vagina is very narrow, I use a special instrument that does not require dilatation with the speculum.

In pregnancy there are no contraindications to perform colposcopy and target biopsies, but the biopsies tend to cause slightly more bleeding. Scraping of the endocervical canal should be done only in rare cases, after discussing the potential complications; alternatives should be preferred whenever possible.

**Is there only one method to perform colposcopy?**

No, there are two main methods: one follows three steps and the other only one. The single step method with acetic acid is adequate to identify precancerous lesions, and it requires less time. I use the expanded method because, in a few more minutes, I can get a more complete assessment that can help in resolving symptoms and problems. For example: I can detect trichomonas infection without a wet-mount examination; distinguish between infections other than HPV that are at their peak or on their way to heal; identify areas of trauma and scarring, much better than by naked-eye exam; map the response of tissue to estrogen, etc.

**Colposcopically directed biopsies.**

A colposcopist should know how to identify the most advanced area of disease and to take accurate but small biopsies; this ability varies with training and experience much more than the ability to take a pap-smear.

It is sufficient to excise 3-5 mm samples of tissue: such biopsies do not require stitching and are generally not more painful than an insect bite. They heal in one or two weeks, during which period of time it is recommended to avoid sexual intercourse and swimming or bathing, for the sake of preventing infections. Occasionally, multiple biopsies are necessary. In selected cases it might be indicated to scrape the inside of the canal of the neck of the uterus; I prefer to use a special brush that is equally reliable and much less uncomfortable.

The biopsies are processed and read in a pathology laboratory: the report is considered diagnostic (*dia* = completely, and *gnosis* = knowledge); in other words they are the ultimate proof of the presence and degree of a lesion. It is easy to understand that if the biopsies are taken in the wrong areas the diagnosis is misleading. Whenever the pap-smear indicates a higher degree of lesion than the biopsy, the colposcopy should be repeated and a second opinion might be warranted.

## **PART FIVE OF SIX: SURGICAL TREATMENT MODALITIES FOR HIGH GRADE HPV RELATED DYSPLASIA**

The ultimate treatment for HPV is a balanced immune system, but high-grade dysplastic lesions will progress to cancer if left untreated. In all high-grade lesions, and in other selected cases, it is appropriate to surgically remove all or part of the dysplasia. The modalities that are available at present can all be successful, in the hands of experienced operators; when misused, they all can produce negative side effects. Here is a brief description:

**Chryosurgery:** this procedure can be performed at the office under minimal local anesthesia, and destroys tissue by freezing. It is still popular because it is very fast, relatively cheap and does not require very sophisticated equipment.

On the negative side there are several considerations: the healing is prolonged and characterized by a very abundant discharge; the tissue destruction cannot be monitored and tends to be more extensive than necessary; if the lesions are deep inside the cervix it is possible to end up with a scar covering areas of disease that will progress without being detectable by pap-smear / colposcopy; the opening of the cervical canal can be narrowed and the production of mucous impaired with decreased fertility; very extensive destruction can result in poor healing, with pain or bleeding during intercourse. Last but not least, no tissue is available for pathologic examination.

Suggestions: ask to see the probe that will be used for the procedure; ask specifically why this probe and not another type was chosen; if you desire to have other children ask why this method and not another one should be used; if the disease reaches inside the cervix, refuse to have this method used and ask for a second opinion.

Refuse to have chryosurgery if the lesions extend to the vagina, because the vaginal wall is very thin, the bladder or the rectum can be injured, and permanent scarring, mostly in the deeper vagina, can be painful.

For condylomata of the vulva and perineum chryosurgery can be an option if done with special, small needle-like probes.

There is nothing doable by chryosurgery that could not be done better by one of the other surgical techniques.

**Loop Electrode Excision Procedure (LEEP):** as the name describes, the tissue is excised using a fine metallic wire powered with electricity. Like chryosurgery it can be performed in the office under local anesthesia. Unlike chryosurgery, this procedure is performed under colposcopic guidance and the extent of excision is well monitored.

The excised tissue is available for analysis by the pathologist.

If lesions are deep inside the cervix, and a very deep excision is necessary, the uterine neck might be weakened and not be able to hold a pregnancy to term.

*Bleeding, comparable to a small menstruation, is common after LEEP but, in my opinion, preferable to over-cauterization that might result in excessive scarring and tissue distortion.*

Healing takes approximately six weeks, and it depends on the quantity of tissue excised, the presence of infections, and the hormonal status.

**L.A.S.E.R.:** is a procedure that utilizes the power of a beam of accelerated light resulting in selective tissue destruction. It is often performed in the outpatient surgical facility, because of the space and safety precautions required by the machinery.

The lesion can be completely destroyed (*vaporized*) or excised. When the lesions are small and superficial LASER excision would destroy more tissue than a LEEP or cold knife technique;

on the other hand, it is possible to obtain by LASER an accurate deep cone of tissue from the cervix.

*LASER is applicable to all surfaces and cavities, and it is the procedure of choice for vaginal lesions and for extensive lesions of the vulva and perineum. With rectal lesions one has to take precautions to avoid explosions due to the interaction between CO2 LASER and intestinal gas.*

Healing depends on the extent of treatment, presence of infection, and hormonal status; under normal circumstances it takes approximately six weeks.

**Traditional Surgical Excision:** is always an option, for all sites. The tissue obtained with this method is the best preserved, without heat artifacts that might make interpretation by pathologists very difficult after LEEP and LASER.

Large excisions require sutures and healing takes more than six weeks

**Partial Excision or Destruction:** in certain situations, taking small multiple biopsies, or selectively destroying by whatever technique small portions of a larger lesion, will start a process of healing and a reaction of the immune system that can bring to complete elimination of the non-excised portions.

Close monitoring by experienced physician is mandatory.

## PART SIX OF SIX: COMPLEMENTARY TREATMENT METHODS

### CHEMICAL METHODS

**Tetra and Trichloroacetic Acid:** like desiccation is feasible only for small, external lesions. The liquid is applied after protecting the surrounding skin with an ointment. Might require several applications and might take weeks to complete.

It is generally applied in the office.

Approved for use in condylomata, not in precancerous lesions.

**Podophillin:** FDA approved for self-application only to external lesions. It seems to be more irritating than Imiquimod, producing erosions in more than 30% of cases. Must be applied twice daily, in cycles of three days followed by four days of rest. The week-cycles need to be repeated up to four times. The local side effects resolve in 10 weeks.

Approved only for treatment of condylomata; has a 70% rate of resolution. Contraindicated in pregnancy.

**5fluorouracil:** an antimetabolite, not an antiviral agent, it can be applied in cream to vaginal and cervical lesions. Contraindicated in pregnancy because of known cancer inducing and teratogenic properties. Not only the vagina but also the external skin can be severely irritated or ulcerated by the discharge and a tampon is generally used for protection.

It is indicated for precancerous lesions, rarely used for condylomata.

**Cidofovir:** FDA approved only for use as intravenous antiviral in subjects with deficient immune system (HIV) and high risk of cancer. The side effects are multiple.

Therapy should be prescribed and monitored by specialized physicians. See also “Off Label Use”

### IMMUNOLOGIC METHODS

**Interferon Alpha:** injectable interferon alpha is FDA approved for treatment of both internal and external lesions. Injections are painful but tolerable and can be done in the office under minimal sedation. They provide an immune factor that has strong antiviral properties.

The systemic side effects are frequent and include a flu-like syndrome that can last for several hours, to a few days. Contraindicated in pregnancy.

Used for both condylomata and low-grade precancerous lesions. Resolution should be monitored closely and it does take several weeks.

**Imiquimod:** it is sold in a cream form for self application to external lesions. This product increases the natural production of skin interferon.

It might give local irritation and, in rare cases, ulcerations with a generalized flu-like reaction. It is applied every other day or every third day. The treatment must continue for eight to twelve weeks or longer.

Sexual intercourse in the days of no application is not contraindicated, according to the manufacturer’s instructions, but it is often very uncomfortable.

Primarily indicated for condylomata, but it can be effective in precancerous lesions too. See also “Off Label Use”

## HOMEOPATIC REMEDIES AND NUTRITION

(recommended only for low-grade dysplasia, They can be used as adjunctive treatment for high-grade dysplasia)

**Iscador:** is an injectable extract of *Viscum album* (mistletoe) has been used as antiviral and antineoplastic for a long time. A study from the University of Pavia (Italy) demonstrated that it might induce regression of HPV-related lesions. Side effects are generalized flu like symptoms, in a few cases, and redness with mild discomfort at the injection site.

**Indole-3-Carbinol (I3C):** is a compound extracted from cruciferous vegetables (cabbage family). Taken by mouth in doses of 200 to 400 mg a day can produce regression of HPV-related lesions. Only small studies are available. No negative side effects except some bloating have been reported.

Preliminary reports from the Linus Pauling Institute, in 2000, warned that in certain animal models, I3C supplementation after cancer is established enhances its progression.

**Retinoic Acid:** a derivative of vitamin A (retinol), if applied to the cervical lesion might produce regression of mild to moderate HPV-related lesions. In a prospective study no effect was seen on severe dysplasia (CIN3).

**Cabbage and the alike:** broccoli, brussels sprouts, cauliflower, etc must be eaten in large quantities to match the 200 to 400 mg dose of I3C. One third of a medium head of cabbage per day would be equivalent to approximately 400 mg.

Ingesting these large daily quantities might interfere with thyroid function, due to other cruciferous vegetables components.

**Beta-Carotene:** studies have failed to support a positive effect on HPV-related lesions.

**Folic Acid:** improving folic acid levels does not correlate with regression of HPV-related lesions.

## OFF LABEL USE AND RESEARCH PROTOCOLS

**Cidofovir:** Studies at the University of Bruxelles, (Belgium), have utilized Cidofovir in a gel form and demonstrated up to 50% regression of high grade precancerous lesions of the cervix.

Approximately 20-40% of women do develop ulcerations that tend to heal in several weeks without leaving areas of tenderness nor scars.

**Imiquimod:** many physicians in the US have started to offer this cream as self- treatment for vaginal use, even if it is only FDA approved for use on vulva and perineum.

Regression of vaginal and cervical lesions has been anecdotally reported.

Ulcerations and occasional flu-like reactions happen in a large minority of cases. Like with Cidofovir, the ulcerations heal over several weeks without scarring.

**Study Protocols:** can be joined when available.

## **RECENT NEWS ON THE HPV VACCINES**

### **What is a vaccine against HPV?**

Purified virus particles that are no longer capable to create infection or cancer, but can create a strong immune reaction against HPV, protecting from real infections.

### **Are vaccines all the same?**

There are two vaccines, so far, tested in humans. Both are effective and well tolerated. One protects from HPV types 6-11 (low risk that account for 90% of genital warts) and 16-18 (high risk, responsible for 70% of HPV related cancers).

The other protects from types 16-18 only.

### **How are vaccines administered?**

Both vaccines must be injected intramuscularly. Repeated doses, up to a total of three given over a six months period, might be necessary to complete the immunization. A second generation vaccine that could be administered orally is under investigation.

### **How effective are these vaccines?**

The follow-up studies have been conducted only for two years (and we consider this a “short period). Studies are ongoing to verify if protection persists in the long period.

Very effective against dysplasia: only two cases of high-grade dysplasia in 12,000 women age 18-25 years, over 24 months of follow-up.

Excellent protection against warts: no warts in the 2,717 women treated, and 40 cases in the 2,725 untreated women.

### **Will the pap smear be necessary for vaccinated women?**

Vaccination will not replace the pap smear until our knowledge of the effect and the long term results will be clear, and this might take more than a generation.

### **When should the vaccine be administered?**

Before sexual contact begins. But also sexually active women with negative HPV test could benefit.

### **Should males be vaccinated?**

They are affected by HPV infection and contribute to spread the disease to their partners. Male should be vaccinated, like females, before the beginning of sexual activity, but costs appear very high.

Male vaccination on a voluntary basis will hopefully be encouraged.

### **When is the vaccine going to be available in the US?**

By the late Summer or the end of the year 2006.

### **Who will administer the vaccine?**

Governmental policies have not been issued yet.