

Recurrent Respiratory Papillomatosis NEWSLETTER

Vol. 15 No. 1

An RRP Foundation Publication
P.O Box 6643, Lawrenceville, NJ 08648-0643
www.rrpf.org

2006 Fall

This issue of the RRP Newsletter is dedicated to **Kaitlin Redmond** (13 months) and **Keely Hager** (18 years), both of whom have recently passed away from complications associated with their RRP.

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From the Newsletter Coordinator and Editor

The RRP Foundation has been supporting and networking the RRP community for more than a decade and wants to continue to be responsive to the needs of the RRP community. In this regard we would appreciate any comments you may have regarding the RRPF. **The best way to let us know what you are thinking is by email to one of the members of the RRPF Board, i.e., Chris Neuberger, Maura Weiner, Susan Woo or Bill Stern,** (see addresses listed in the section on “Organizational Information”).

We continue to seek additional help in preparing, editing and coordinating the publication of the **RRP Newsletter**. In

particular, we are asking for a volunteer to take on the lead role of coordinating and publishing future issues. If you are interested in assisting in any way, please contact **Bill Stern** (bills@rrpf.org).

We hope you find this newsletter issue to be interesting and helpful.

We are most grateful to all those individuals, medical professionals and corporations who have supported the **RRPF**. Although it is impossible to publish the names of all who contribute, we extend our sincere thanks to everyone who has supported our efforts. Future donations from individuals, professionals or from the business community will be very much appreciated.

Tax-deductible contributions may be made to:

RRP Foundation
P.O. Box 6643
Lawrenceville, NJ 08648-0643

Do you donate to the **United Way** through your employer? You can select a "Donor Choice" option, which would allow you to direct a donation to the **RRPF** as the 501 (c) (3) of your choice. Since the RRP Foundation is a 501(c) (3) foundation, you may specify the RRP Foundation directly by writing in the name and address of the foundation as follows: RRP Foundation, P. O. Box 6643, Lawrenceville, NJ 08648. If you should need to add our Fed. ID number, it is 521798693. Thank you for your support.

Donations accepted online via Pay Pal
From the RRPF home page (www.rrpf.org) or go directly to
<http://www.rrpf.org/donate.htm>

Special Acknowledgments

We once again want to acknowledge the generous efforts of Ed and Maura Weiner along with their friends for a very successful **4th Annual RRP Hockey Night** fundraiser for the RRPF.

And

We would like to thank **Medtronic Foundation** for its generous grant to the RRP Foundation patient support program.

To physicians and nurses: Please distribute copies of this newsletter to your RRP patients. Please register with the RRPF by completing the Practitioner Questionnaire (online or copy enclosed).

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RRPF Publication and Subscription Policy

The **RRPF** produces two publications, the *RRP Newsletter* and the *RRP medical reference service*. The *RRP Newsletter* focuses mainly on the human and clinical aspects of recurrent respiratory papillomatosis and in this regard targets a broad readership, including patients/families, attending physicians/nurses, as well as researchers and the general public seeking to stay in touch with RRP from a clinical perspective. The *RRP medical reference service* serves those in the community seeking a more comprehensive understanding of this disease. Please help us by supporting these publications and other RRP services including patient outreach, support, advocacy and research.

Subscription Policy and Suggested Minimum Annual Donations:

RRP Newsletter
Professional/Corporate - \$25
Individual - \$15

RRP Newsletter plus Medical Reference Service
Professional/Corporate - \$40
Individual - \$25

[Note: Issues of the *RRP Newsletter* and *Medical Reference Service* are available on the website.]

RRP Network News

Our international support network has grown to approximately 800 respiratory papilloma families. Patients range in age from about 2 to 88 years. Domestically, patients are located in 48 states plus the District of Columbia. Outside the U.S. there are currently 33 patients from 14 countries.

Our thanks to all who have taken the time in the past to fill out the **RRPF Patient/Therapy Survey**. There is now a new **comprehensive RRP patient survey available online at <http://www.rpfp.org/rpfp/survey>**. So even if you have already completed a survey, help us to learn more about this disease by **taking a little time to complete the new survey**. Please make sure to alert us of **changed addresses** by checking the "new address" box. There is also a box which we ask you to check if you do or do **not** want your name and address information to be included in the RRP Patient Directory. We are requesting the information contained in this survey be made available for RRP research. In this regard there is a place in the beginning of the survey to grant permission.

As our support network has grown, we have become more dependent on the patient questionnaires to maintain our mailing list and keep our database of RRP patient information up to date. If you are updating a previously filled out questionnaire, you need only identify yourself, and answer only those questions where you have new or updated information to provide. This is also the case for the new comprehensive survey, just make sure you specify the **patient's first and last names and their year of birth**.

Doctors and nurses treating RRP patients take a few minutes to fill out the **practitioner survey form**.

You can find the online "patient survey" and "practitioner survey" respectively on the "patient" and "practitioner" page links from the RRP home page (www.rpfp.org).

RRP Web/Internet News

by Bill Stern

The Internet is now the most often used information exchange for the RRP. **Our website (www.rpfp.org) has recently been redone with a totally new look**, which we hope will make finding information easier. It contains a wealth of information relevant to patients, families, doctors, nurses and researchers. It includes an **online database of RRP practitioners** (updated through January 2005). The website has a **new Interactive Discussion Forum** which allows for the posting of questions, comments and replies to previous postings relevant to RRP. We also have the **RRPF Email Listserve** (see below), linked to the home page. As noted above, you can find the **new RRP Patient/Therapy Survey** and **RRPF Practitioner Survey forms** on line, which allow RRP patients and caregivers to easily submit their survey to the foundation. This is a very important aspect of the Foundation in that this information is used in analyzing RRP treatment therapies, experiences, etc. We ask that patients and practitioners update their survey at least once a year.

Also, we maintain an online library of **RRP Newsletter** and **RRP Reference Service** issues plus links with many other sites relating to RRP and much more.

If you have some **experience/expertise with the WWW** and would like to help us improve our website, **please contact Bill Stern**.

RRPF Listserve Highlights

by Randy Sparkman

Since its creation in 1999, the RRPF-sponsored e-mail distribution list has grown to over 400 members. The list continues to serve as a valuable source of information on the diagnosis and management of RRP. But it has also emerged as a vibrant community where patients and caregivers can share experiences and support.

Over the past year, the mailing list has generated 3-5 messages per day. These threads have included discussions of patient experiences, various treatment options, risks and success rates, discussions of treatment centers and resources as well as environmental considerations. Extensive discussions have taken place regarding the new HPV vaccine, its safety, efficacy and possible impact on RRP. There have been a notable number of interactions between researchers and patients. All communities are well served by these discussions.

Listserserve users should be aware that the RRPF e-mail list is vulnerable to the same issues as all on-line services. Access to the list archives is limited to only those users who have registered with the hosting service, YahooGroups. But participants in the list should not assume any privacy of information posted there. Anyone can register for Yahoo Groups, for free. Subscribers with privacy concerns should not post full names, postal addresses, e-mail addresses, etc.

Users should also protect themselves and others from computer viruses. Users should not forward e-mail attachments to the mailing list and should not open any attachments within messages received from the list. This does not mean that the mailing list increases the risk of receiving a computer virus, it is simply good practice to delete e-mail messages with attachments unless you are absolutely certain of the identity of the sender and the content.

Basic subscription information and complete list archives are available on the Internet/World WideWeb at: <http://groups.yahoo.com/group/rpfp>. The messages may be generated and received from within your e-mail computer client or can be completely generated and received from the yahoogroups rpfp list web pages. Messages may be received one at a time or in a "daily digest". Anyone within the RRPF community that needs technical assistance with any aspect of the mailing list can send an e-mail to: jubrising@gmail.com

RRP Patient Profile

First an introduction, my name is Kelly and I am 27 years old. I live in Halifax, Nova Scotia, and have a rare form of what people refer to as “a not so bad disease”, papillomatosis. I was diagnosed with it at age 4. Since age four there has been too many operations to count (I believe we lost track around 100 quite a few years ago). The disease is most common in children and its progression is said to slow down, even to stop altogether once the juvenile in question reaches puberty and the body’s hormone levels adjust and change. As I explained, I am 27 and still fighting this “not so bad disease”.

This is where you come in. This is a cry for help. I need something to inspire me, help respark the hope within me and renew the desire to keep on fighting.

As far as treatment, I have only ever had laser surgery. I have never talked to anyone else suffering from my disease and have developed severe panic attacks revolving around the operations. My ENT specialist is very caring but I have so many questions and he has very few answers.

I definitely feel selfish writing this letter, as I know there are people who are worse off than myself. But honestly I am burnt out, I am not sure how much fight is left within my heart. I have been fighting what others perceive to be a manageable “not so bad disease” for 27 years.

I struggled with this disease from birth, long before it was diagnosed. My mother has been my angel from day 1 sensing trouble with my crying and breathing from the minute she took me home.

My mom, was concerned that her baby girl wasn’t living the happy healthy life a newborn deserved, the life that she was determined to give her. Essentially her perseverance, however annoying to the doctors treating me, SAVED MY LIFE.

My Mom’s Story

Shortly after bringing my daughter home from the hospital, I discovered her difficulty when breathing and the odd sound of her cry. The doctors repeatedly told me I was being an over active new mom. I did not agree.

For 4 long years, I harassed the doctors and, pushed and pushed them; until finally they decided to humor me by taking her into the operating room to see if there was something going on with her throat after all. We (being her parents) waited with great anxiety outside the OR; we didn’t wait long however, within minutes the doctor came out and said he would see us in his office in an hour. They brought my child out to me and said nothing more.

The anticipation was overwhelming. We rushed her home and then went to the office where we were told she would need surgery immediately, that the growth in her throat was closing her air way. We were told to take her to Halifax (the biggest city in our small province of Nova Scotia) where there was a specialist who would remove the growth.

Well here it is 24 years later and she is still having surgeries, although they have gone from being every 6 weeks with a 2-day trip to the ICU unit (throughout her childhood), to being able to have the surgery and go home the same day.

Today the surgeries are better and the stay in hospital shorter, however, the trauma is much greater. You see Kelly now suffers from extreme anxiety, panic disorder which developed as a direct result of the many devastating surgeries and the lack of compassion from not only cruel children who

made fun of her constantly throughout her childhood but from nurses poorly equipped to deal with Kelly’s level of fear and anger at the amount of operations she was forced to endure at such a young age, and then on into adulthood. She does sound and will always sound as if she has a cold. Each surgery is now more traumatic than the previous one and the so-called professionals that work with her do not understand her fear nor do they try to understand the panic. As her mom, I have spent my life feeling guilty and sad that somehow I did this to my child. Even today I do not know what more I can do to make her life better. It is very draining and I pray that with God’s help you can finally help Kelly find some sort of peace surrounding the treatment of her disease, as there is still no end in sight.

Back To My Impute

This afternoon I had a perfect example of why my disease supposedly “one of the better diseases you could have” wasn’t such a day at the beach.

The first stage of the day may be described as almost pleasant, I mean as pleasant as one could expect given the circumstances. Those circumstances being, that I am about to be put under for well over my hundredth procedure each exactly the same as before, however the hospital has a few unsung heroes who find just a few minutes to make the day more bearable. This would include anyone who has been with me through it all, my doctor and some of the nurses who remember carrying my terrified, trembling little body into the OR. Now they hold my hand and offer true empathy and compassion as I lie, a little bigger now, terrified and trembling still.

You think, due to my experience with this procedure and because of trial and error, when it comes to what does and does not work well during the procedure, I would be given some credit or say in what I need after all these years.

Keeping with the giving credit where it’s due, I have to say a lot of people involved in my case at one time or another humor my requests or at least take the time to calmly, gently explain the alternatives. It is these generous souls who have made these experiences bearable up do date. Most of the staff that knows of me or has treated me over the past 27 years knows the trauma and anxiety levels that take over (If you’ve never experienced one “take over” is a pretty accurate word to describe just how little control you have of what is taking place with your body).

There are levels in my case, to how severe my attack can get. **Here is where the trauma begins.**

I have spent years conferring with psychologists, psychiatrists, my ENT, clergy, prayer, self-help books, and through this journey realized the solution was simpler for me. I need to feel safe in order to avoid the panic attacks.

I feel safe with my ENT doctor by my side, my mom by my side and there are even a few key nurses who have throughout my journey lent me their compassion,

Understanding my fear and terror are real and the symptoms just as intense as if brought on by a non-panic situation, I cannot stop them on demand. I am not faking or looking for attention, truth be told, if you asked me what I fear most in this world, it is the panic attacks and how real and devastatingly they affect me.

I am the first to admit that doctors and nurses are too busy, and have even sicker than me to tend to, so a few years ago we (my support team and I) had it worked into my file (or thought we did) that if I start to feel anxious and ask for my mother they were to allow her against policy, into whatever the restricted area, to be by my side and help prevent the more horrifying stages of the actual attack.

When an attack is coming on I start feeling anxious, my skin feels tingly, I begin to hyperventilate, my heart starts to beat erratically, sometimes I faint or urinate myself. Sometimes my muscles become rigid and even paralyzed, sometimes times I can't speak. The not speaking symptoms are a bit less painful than the alternative, because when I loose control of my emotions and the crying starts the vocal cords in need of rest after their recent surgery become strained with terrified tears and begging for my mother to save me from what feels in that moment to be a life or death situation.

Today after the procedure I began experiencing some slightly different symptoms that can be scary after over a hundred procedures without this symptom. The explanation was simple and I was appeased, however the anxiety had already started and the nurses' comment that "you need to get over this and just stop," didn't help. Through labored breaths I asked for my mom explaining she knew what to do. I also pointed out a note that I made sure existed on my chart saying "get mom at the first sign of trouble." The nurse then replied "if you can get this under control for mom, you can get it under control for me, I am a nurse. Stop hyperventilating now and breathe."

Things just kept on progressing from there and I suffered a terrifying indignity that may well have been avoided with a little compassion for the terrified little 27 year old girl that still needs help dealing with this "not so bad disease".

You may be wondering what can you do. Well any support would help I am at a loss and in need of guidance. ... honestly I am about ready to give up. It is just emotionally tearing me apart. Also, because of my severe panic reactions to the surgery, I find my post operative care by the nurses only adds to the trauma of my disease.

I want you to know that the part of the story told to you today is only a part of me. Panic disorder does not control my life. It just takes over for a few hours maybe days, a few times a year during treatment for my "not so bad disease".

The rest of my life has been the best I could make it. I wanted to see the world with no money so I joined the cruise ship and resort industry. I worked hard at these jobs but gained confidence and a sense of others and a sense of their challenges and formed lasting supportive relationships all over the world.

I am enthusiastic and caring and would honestly give up anything of myself to save anyone from anything even resembling the pain I have endured through my "not so bad disease".

Others describe me as outgoing, and quirky and I would like to preserve that part of me before I loose my fight and anxiety and depression start creeping around into non-hospital related parts of my life.

As my age progresses, thoughts of having children terrify me. Is there any chance I could expose them to this? I have so many questions; I have been crying since Friday after my latest treatment and haven't convinced myself there will be a next treatment, because when I left that hospital today I had given up. I wasn't going back, not to face the horrors and fear again. This "not so bad disease" should allow me quite a few years of trauma free life before becoming truly life threatening (the nodules would eventually cover my airway) and I would face that possibility of death when it stared me in the face.

That's not me though, that is the fear talking. I fear the panic and I fear my uncertain future concerning this disease.

I am open to suggestions; I am willing to try anything.

The truth of the matter is in 6 months I will be expected to walk through those operating room doors once again and right now I can't honestly say I'm up for that fight.

Kelly
ktarso@hotmail.com

RRP Patient Stats

Please complete or update the comprehensive RRP patient survey available online at: <http://www.rrp.org/rrpf/survey>

Very preliminary statistics may be viewed at:
<http://www.rrp.org/rrpf/survey/update/admin/>
user = "rrpf"
password = "Foundation" (case sensitive)
(Caution: These are "raw" stats and in some cases may not make sense.)

Support and Fundraising Activities

[For support of new RRP research initiatives, please see section on "Science and Research Activities"]

Support for RRP patient related travel expenses:

The RRPF has dedicated a limited amount of funds to provide indirect support of some travel expenses to obtain treatment for RRP families truly in need. If you would like more information please contact:

Geni Mesi
5780 Village Way
South Ogden, Utah 84403 (801) 695-0108
e-mail: mesifam@hotmail.com

Fundraising Activities:

4th Annual Hockey Night for RRP

On Saturday night, January 21, 2006, Ed and Maura Weiner held the 4th annual Hockey Night Fundraiser for RRP in Washington DC at the MCI Center. Ed and Maura netted the RRP Foundation over \$10000.

Running For RRP

On January 7, 2006, Julie Bowne and her sister ran the **Disney half-marathon** in Orlando, Florida. Julie's and her sister's efforts helped promote RRP awareness and raised over \$2000 for the RRPF.

On April 30, 2006, RRP Foundation Director, Bill Stern ran the **New Jersey Marathon** for the second time to raise awareness and funds to support RRP research and networking between patients, physicians and scientists. Donations for this event came to about \$1000.

RRP Meetings

!!! Future meeting !!!
RRP Focus Session 2007
Washington D.C.
Tentative date is Saturday, 15 September, 2007
More details will follow
Check rrpf.org / RRP F Listserve
!!! Mark your calendars !!!

HPV 2005 Forum on Education and Advocacy RRP Session Summary

The RRP Education and Advocacy Session took place in Vancouver, BC at the 2005 HPV Conference on Thursday, May 5th, 2005. The program was jointly sponsored and coordinated by Michael Green of The International RRP ISA Center and by Bill Stern of The RRP Foundation. A session summary follows:

1. Biology of RRP: Role of Cox 2 – Bettie Steinberg

RRP Biology - RRP prevalence in society stands at 1 case per 100,000. Malignant conversion takes place in 3%-5% of all RRP cases (increases to 30% when Papillomas are treated with radiation). If Papillomas enter the lungs, malignant conversion increases to 80%.

RRP prevalence stands at 1 case per 100,000 in population. The incidence (or new cases) is projected to run 5 per 1,000,000.

RRP is typically caused by HPV type 6/11. A number of adjunct therapies have been used over the years with some new therapies being investigated. The newest therapy under investigation by Long Island Jewish Hospital involves the use of Celebrex (Cox 2 inhibitor).

Life Cycle of RRP

HPV virus enters the normal epithelium (in most cases of virus exposure this is where it stops). However, in cases that become RRP, the virus penetrates to the basal layer. It is in the basal layer, where cells proliferate, while the cells in the epithelium shed. Once the virus enters the basal layer, the hpv virus enters a basal cell and begins to reproduce itself. The eventual papilloma tumor is created, not due to rapidly dividing cells, but rather the cells with hpv don't know they are suppose to die, thus, pile up on the surface as a papilloma.

Cell death-differentiation – Cells are sent signals to cause the cell to die. The signals which do this are altered, which then induce Cox 2 (which is turned on in tumors and inflammation).

Studies in mice have shown that in mice which exhibit Cox 2, that mice get skin tumors. Cancer prostoglandins, made by Cox 2, suppress the immune system, increasing tumor growth and suppress cell death.

Preliminary data has shown that if Cox 2 is inhibited, proliferation goes down and cells die. The higher the dose, the more cells that die.

LIJ has designed a study of Celebrex that will be a multicenter randomized placebo controlled study. The study will be for adults only (18 years or older), who have surgery at least three times per year. It will have two start times 6 months and 18 months after enrollment. There will be six months of observations/surgeries, and then participants will be randomized. Some will receive 400 mg of celebrex daily, while the others will receive placebo. The placebo group will later receive the celebrex. In addition, provisions have been made to unblind the study in certain situations (patient exits, remission, etc). Patients will take celebrex for one year, then crossover. Disease will be scored via endoscopy for a period of 2.5 years.

2. RRP ISA – Michael Green

Michael Green presented information about the RRP ISA Center and the work that is underway. RRP ISA is actively involved in research and patient advocacy. Michael also discussed the interactive patient database that provides real time analysis of the information. The website is www.rrpwebsite.org. In addition, the RRP ISA is actively seeking grant proposals for funding requests. Funds are available to support worthwhile research.

3. RRP Foundation – Bill Stern

Bill Stern presented information about the RRP Foundation, outlining the history as well as development of the organization. The RRPF currently has in excess of 750 patients in the database. In addition, a web based system using a Lagrangian Approach for Collecting RRP Epidemiological Patient Data was discussed. This database was developed with the help of Tom Mingot. The RRP Foundation is actively seeking grant proposals for funding requests. Funds are available to support worthwhile research.

4. Efficacy if different acyclic nucleoside phosphonates in organotypic epithelial raft cultures and cervical xenografts inathymic nude mice – G. Andrei (presenter) J. Van Den Oord, I. Lebeau, G. Wolfgang, W. Lee, E. De Clercq, R. Snoeck

Dr. Andrei noted that 630 million individuals worldwide are infected with HPV, this translates into 24-40 million in the U.S. with 2,000 – 2,500 new cases per year. 6,000 children per year are treated.

The use of cidofovir is being used to treat HPV infection. Current intralesional dose levels range from 2.5 to 7.5 mg/ml, up to 10 mg/ml. If cidofovir is injected in uniform intervals, the results have been better. The best response (RRP usage) has been in the supraglottic and glottic regions. Cidofovir is injected into the disease site until resolution of disease, then an additional injection is given. The more severe the disease, the better the response has been. Intralesional injections are far below levels of toxicity, and to date there have been no reported problems with the use of cidofovir.

5. Preliminary analysis of a 10 year retrospective review of RRP patients – P. Campisi

Dr. Campisi is a pediatric otolaryngologist in Canada. Dr. Campisi reviewed some background information on RRP. Canadian pediatric RRP patients are generally treated at 1 of 3 hospitals in Canada. It is his goal to establish a Platform for

Canadian Registry and model it after the former CDC National Registry for RRP. It is believed that it will be much easier in Canada, since the majority of the patients are treated at a limited number of facilities. In addition, once the patient outgrows the children's hospitals, the adults are also treated at a limited number of facilities. This would simplify data gathering and fact analysis.

Dr. Campisi would also like to launch a surveillance study for the HPV vaccine.

A portion of the presentation was also devoted to the microdebrider and a discussion about the medical system in Canada.

6. RRP Round Table Discussion – participants- Bettie Steinberg, Keerti Shah, Tom Broker, Craig Derkay, Tom Mingot, Michael Green, Kathy Blankenship, Bill Stern, Chris Neuberger

The participants introduced themselves to the audience.

Dr. Shah, raised the issue of a study to look at the efficacy of the HPV vaccines (once released) of new cases of JO RRP to survey if the birth mother was a recipient of the HPV vaccine. It is expected (in theory) that new cases RRP should become extinct with the introduction of the vaccine.

Dr. Broker provided a summary and update of the HPV Advocacy sessions that had been held over the course of the week. A grass roots effort is what is needed as politics are local and the politicians are the key in changing public opinion and generating necessary funding. The medical and research community need to dialog from the professional community as well. In addition, there are a number of HPV organizations and there is a need to tie together these organizations for advocacy. A website that disseminated the information and worked to coordinate the variety of HPV organizations was discussed as well.

There is a great need to de-stigmatize HPV and the consequences. It was noted that dealing with the disease outcome, such as cervical cancer would help to de-stigmatize. It was also noted, that Cervical cancer is a different focus by different cultures. There are many local and cultural barriers that need to be overcome in order to do this.

Dr. Derkay discussed a study that is proposed to analyze the viral load in the saliva of children.

Summary of Spring and Fall 2006 RRP Task Force Meetings

Minutes prepared by Craig Derkay, MD
summarized below by Bill Stern

The Spring Task Force meeting took place in May, in conjunction with the AAO Spring meeting that was held in Chicago. The Fall Task Force meeting was held in conjunction with the AAO annual meeting in Toronto.

Some of the topics discussed were:

1) **Update on HPV vaccine efforts** – With the approval of the Merck HPV vaccine Gardasil, there was much discussion about the role that this vaccine may have with RRP. In particular:

(a) Therapeutic possibilities -
Indications from Drs. Campisi and Rosen, who attended Merck investigators meeting in July, are that Merck is not likely to fund a wide-scale trial using Gardasil therapeutically. Discussions followed regarding possible pilot studies applying Gardasil intralesionally in active RRP patients, intramuscularly to patients in remission and using the vaccine in patients with involvement outside the larynx. There was a consensus to try some therapeutic application in a coordinated way.

(b) Preventative possibilities –
Dr. Froelich, attending the HPV meeting Prague met with Aventis/Pasteur (they own European rights to Gardasil) and is optimistic about a surveillance/epidemiology study of the preventative/therapeutic benefits the vaccine being organized.
Discussed the possibility of using the vaccine in pregnant patients (not likely in US) and in newborns at-risk of acquiring an HPV infection.

2) Research Initiatives –

(a) HspE7 Phase III trial is currently on hold, as Stressgen has gone through some corporate changes and is now Nventa Corp. They are still tentatively planning a trial but may not happen for 2 years.

(b) Celebrex study at LIJ continuing with a reduced dosage (to allay any cardiac fears). RRP patients currently enrolled only at LIJ, but hoping to expand to 6 sites.

(c) Dr. Buchinsky provided an update on his RRP genetics study. They have expanded the pool of patients via collaboration with patient support organizations and currently are investigating 4 candidate genes.

(d) ICTV (a topical agent that has shown promise in treating plantar warts) is being formulated for potential use with RRP.

(e) Dr. Campisi is currently working with colleagues in Canada to create a registry of RRP patients there. Similar registries are being proposed in the UK and Sweden.

RRP Focus Session 2005 Highlights

The RRP Focus Session is an event that is often convened in conjunction with the American Academy of Otolaryngology-Head and Neck Surgery (AAO) annual convention.

The following is a summary of material that was shared at “**RRP Focus Session: Thinking Outside the Box**” event in Los Angeles on September 24, 2005.

About 45-55 RRP patients and their families attended, along with about 10-15 physicians and researchers in addition to those who were speakers. Four lay people presented and the other 8

speakers (counting Mark Shikowitz who was inserted into the agenda at the meeting) were physicians or PhD level researchers.

The meeting was very well-received and stimulated a great deal of discussion at the dinner afterwards in honor of the speakers.

The following summaries are presented as highlights only. Details are provided in the PowerPoint and MP3 files available on the web at: http://www.rpf.org/RRP_Focus_2005.html

Readers are strongly encouraged to listen to the MP3 recording and consult the PowerPoints for more information.

Generous support for this meeting was provided by **Medtronic Corporation** and **Stressgen Biotechnologies**.

Craig Derkay, M.D.- "Update on RRP Research 2005"

Adjunct Therapy Update:

1. Cidofovir
 - a. University of Pittsburgh Study – Retrospective Study- Method included debridement followed by injection of cidofovir into papilloma sites. The scores were much lower for the cidofovir group; however, the end results were not significant.
 - b. Clark Rosen, M.D. – Study included 13 adults and 3 kids. 10/13 are in remission, 1 did not respond, 1 relapsed. The mean injections were 3.5 and the group was followed for two years. Three were later found to have vocal scarring due to disease or drug.
 - c. Peak Woo, M.D. – Monthly interoffice injections (7.5 mg/ml in office) administered every three months. All five patients had a partial response.
 - d. Smith, M.D. – University of Iowa – 28 year old non-smoker injected with cidofovir 3x over 24 months experienced worsening dysplasia.
 - e. RRP Task Force Recommendations – Cidofovir is appropriate for patients with moderate to severe disease (defined as surgical intervention 3x or more per year). In addition, cidofovir should only be given with patient consent. Not recommended for patients with mild disease.
2. Interferon
 - a. Cuba Study-169 patients – 85 kids/84 adults. Frequency of relapse declined ~75% in group. If given at first papilloma surgery 66% had a complete or partial response to interferon. 75% concluded study without lesions and 25% had reduced lesions.
 - b. Germans have a multi-center trial underway. 42 patients enrolled with a complete response of 43%.
3. Photo Dynamic Therapy (PDT)
 - a. 17 completed Trial at Long Island Jewish Hospital. 5/15 are in remission. In all five cases, recurrence occurred within five years. Conclusion: not an optimal treatment strategy.
4. HSPE7 Vaccine – Currently in Proposal Stage for Phase III Trial. Expect trial to begin in early 2006.

5. Celebrex – Proposed multi-center trial. Dr. Shikowitz provided a brief summary. The Celebrex dose has been lowered due to the cardiac risks. At the lower dose it is now safe. Dosing is 200 mg 2x per day. Several patients are enrolled. It is postulated that Cox II inhibits the replication of the virus, allows the virus to be exposed to immune system, thus patient's immune system can take over.
6. Vaccines –
 - a. Glaxo Smith Kline HPV Vaccine – This vaccine is a prophylactic vaccine which protects against acquiring HPV 16/18 (which is responsible for 70% of cervical cancers). 99.7% of those vaccinated responded with 90% - 100% protected from persistence.
 - b. Merck Vaccine – Gardasil(prophylactic vaccine) – Phase III is ongoing. It is expected this vaccine will be on the market in 1-3 years. Once approved the suggested order for those to be vaccinated is 10 -13 year old girls, older women and boys/men. The vaccine will not replace pap screening. The Merck vaccine works on the humoral vs. intracellular immunity. However, it is speculated that this vaccine if used intralessionally could stimulate the cellular immunity.
[Ed. Note: In June 2006 Gardasil was approved by the FDA. Currently there is NO evidence for therapeutic effects, although this has not been rigorously tested as yet.]
7. General Items
 - a. Reviewed several reference articles (see slides)
 - b. RRP kids have a lower quality of life due to burdens of disease.
 - c. RRP Biology
8. Risk Factors
 - a. GERD – exacerbates RRP. Control of GERD is important to treatment.
 - b. All patients that had RRP in the lungs failed interferon therapy, and most had HPV 11. Lung infection (approx 5%-8) is a tremendous problem for RRP patients.

Bill Stern, RRPF

Provide RRP Information; RRP Physician Referral; Networking, Emotional and other Support

rpf.org

RRP Newsletter

(http://www.rpf.org/newletters/RRP_Newsletter_Spring05.html)

RRPF Listserve (<http://health.groups.yahoo.com/group/rpf/>) – Provides a forum for exchange of information, ideas, opinions and emotions related to RRP. Currently ~350 members consisting of RRP patients, parents, practitioners and researchers (at least 5% are RRP professionals).

Identify and Address Major patient/family concerns, i.e.,

Diagnosis issues

Coping with RRP

Treatments - surgical and adjunct

Voice - preservation, restoration/improvement

Mortality - pulmonary involvement, malignancy

Disease transmission

RRP Awareness

Are Pediatricians sufficiently aware of RRP?

Coordinate with other HPV organizations to promote greater public (and political) awareness of RRP and HPV

RRP Epidemiology

RRPF practitioner and patient databases (currently >750 patients)

RRP Research

RRP Foundation encourages and supports promising research related to RRP. Some of the studies that have received support from the RRPF involve: RRP immunology; Quality of life of RRP patients; Familial genetics and RRP. Furthermore, the RRPF is interested in additional RRP research including: therapeutic role for HPV vaccines, studies to better assess mechanisms and understanding of various adjunct treatments and new approaches to the treatment of pulmonary RRP.

Michael Green, RRP ISA

Michael told the story of how RRP ISA came to be and he explained how ISA is an acronym for Information, Support and Advocacy. He reviewed RRP ISA's future plans and past activities/accomplishments, which amongst other items have included:

A) Awarding of research grants to two institutions, with others in the review stage. In addition to the past grants, RRP ISA announced it would offer up to \$100,000 in research grants over the next year.

B) A new website that is in development

(<http://rrpwebsite.modwest.com/>).

C) A new message board that was just opened

(<http://www.rpisa.tribe.net>).

D) A new informational brochure on RRP that doctors can give to their patients (<http://www.rrpwebsite.org/brochure.pdf>).

E) RRP ISA's presentation at the International Papillomavirus Society's 2005 convention in Vancouver B.C. last May. Michael presented a synopsis of data from that presentation, entitled "*RRP Patient and Family Data Trends Report*" (http://www.rrpwebsite.org/report_on_the_may_2005_rp_focus.htm).

Lotta Gustafsson, Msc, Phd – Treatment of Papillomas with Human Alpha-Lactalbumin-Oleic Acid Complex (HAMLET) Principle investigator for June 24, 2004 New England Journal of Medicine article on HAMLET, Lund University, Sweden

1. HAMLET is a complex for human milk cells that can be produced artificially in the lab. It works via programmed cell death and Hamlet kills different cells via different mechanisms. 1st study on skin papilloma. This was a double blind study with 10 patients applied 1x per day for 10 weeks. There was a 75% reduction in 88/92 lesions. The placebo results were 15/74. In the open study with 2 year follow up, 85% of lesions resolved. Hamlet is applied topically for skin Papillomas. Future studies will consider RRP and lesions on the cervix. Safety studies are needed before the study can progress. This study also needs additional funding.

Aturo Avila Chavez, M.D. "RRP in Developing Countries" International RRP ISA Board Member and Associate Professor, National Institute of Respiratory Diseases, Mexico City, Mexico.

Reviewed RRP statistics. Estimated 1,500 – 2,000 RRP patients in Mexico. The main problem in treatment is cultural, medical and economic. Voice is not treated seriously and is typically ignored until dysphonia or respiratory problems. Due to the economic issues of health care in Mexico, different levels of medical attention are provided. There are very few centers for specialized medical care. Typically a Dr. will have 80-120 patient visits per day or 10 surgeries per day. There is a 6-8 month wait for surgery. Some patients are forced to wait until complete respiratory distress. Most RRP patients are handled in the public hospitals. Most Dr.'s don't have specialized training for handling RRP. Equipment is lacking. A potential solution is to utilize the RRP ISA as a platform.

Richard Schlegel, M.D. PhD – Developing Research into Effects of Artemesinine on HPV. Professor and Chair, Department of Pathology, Georgetown University Medical School

Artemesinine is a Chinese herb used for the treatment of malaria. It reacts with red blood cells by creating free radicals that kills the malaria cells. This herb only works when converted to DHA. It does not kill normal cells. In the Canine model artemesinine cured the canines from papillomavirus (canine pv, not human) infection. Artemesinine is not an anti viral. It is administered topically. Future studies are planned.

Jennifer Woo, Senior Thesis on RRP, Harvard University

Jennifer is a senior at Harvard majoring in Anthropology. The thesis preparation has included three months of travel interviewing RRP patients, families, researchers and others. The thesis topic was chosen based on interest in RRP and the cultural, economic social and political issues. A few themes have been identified thus far:

- ❖ Voice is part of an individual's identity and when compromised it affects the identity of the person.
- ❖ Redefining the definition of disability
- ❖ Stigma of the disease
- ❖ Guilt by parents regarding disease transmission and how to cope
- ❖ Uniting of strangers for and due to the disease
- ❖ Frustration of practitioners
- ❖ Politics of research – and the hostile political environment

The thesis will be published in April and excerpts will be in the RRP Foundation newsletter and relevant peer reviewed publications.

Gregory McKee, CEO of Stressgen

Stressgen has had success with the HPE7 drug. Stressgen has clinical proof of the concept and is now working on the manufacturing process. The 2nd generation of HSPE7 looks more promising for RRP. It will also be a platform for other HPV diseases. The company was reorganized to focus on HSPE7. Hspe7 is designed to be therapeutic drug. It works by making an antigen that is fused to a heat shock protein. These band together and heat shock shepherds to small peptides, then to dendritic cells. Killer T-cells are programmed, replicate, hunt the HPV infected cells, which are then killed.

- a. The drug comes in a small vial and requires 3 injections (1x per month).
- b. The second generation will target genital warts.
- c. The first generation reduced tumor burden to 20% (80% reduction) The second generation will be design to reduce burden to 0.
- d. Additional testing is required and is in process
- e. Time frame is 2.5 years to be available.

Kathy Blankenship, “What I’ve Learned through my Personal RRP Odyssey”, International RRP ISA Center Research and Volunteer Coordinator

Kathy provided a very emotional and moving story on her personal experience, which included a cancer diagnosis and the removal of her larynx. Kathy shared her perspective on:

The effect her RRP has had on her children and how our children help us to realize what is truly important in life. The importance of RRP ISA and RRPF in providing information, support and advocacy to patients and their families; and the importance of emotional support, health care referrals, case management and patient-friendly websites.

Her experience with discrimination by health care providers. Patients Beware/Caveat Emptor: The expectations RRP patients have of their physicians to use good judgment, provide best care possible, and be knowledgeable about RRP and current treatments.

The need for a patient to do their own research and educate themselves about RRP and its treatment.

The importance of maintaining a sense of humor despite having a life-threatening illness.

In conclusion, Kathy noted that despite the removal of her vocal cords, with the help of RRP ISA, she has learned that she very much still HAS a voice.

Farrel Buchinsky, M.D. “Genetic Susceptibility to RRP: Report on Individual and Family Genetics Research Project” Pediatric Otolaryngologist Allegheny General Hospital Pittsburgh, PA

Update of results to date of this ongoing study of RRP genetics. Huge numbers of the population are exposed to HPV 6/11, however, only a few develop RRP. As a result, genetics play a role in who does and who does not develop RRP. A brief presentation on the genetics was presented. Presently the study has 82 enrollees and their parent (s). This study requires a sample of an individual’s saliva as well as that of both parents (or one parent if both aren’t possible). In the event parents aren’t available, a sample from a

sibling would be beneficial as well. This study requires a very large data sample. It is easy and free. Please consider participating, see the following link for information. www.centerforgenomicsciences.org/RRPGenetics

Seth Pransky, M.D. “Current Issues in the Management of Pediatric RRP” San Diego Children’s Hospital

1. RRP is characterized by multiple surgeries and no predictive therapeutic intervention is available.
 - a. General Treatment – debulk lesions via laser, forceps or microdebrider. Conservative approach is paramount as is protection of the anterior commissure. Severity is a function of the number of sites involved. HPV 11 is a predictor of severe disease.
 - i. The mirco debrider with spontaneous ventilation creates less trauma, however, the con is access to the ventricle and subglottis.
 - ii. The pulse dye laser is new and does not destroy underlying tissue and is very good for sensitive areas. It is not good for bulky lesions.
 - b. Adjunct Therapies – Reviewed quickly due to coverage earlier in the presentation.

Cidofovir – 50% hit rate based on 7 years of history. Non responders are 15%. Dosed at 5 mg/ml with four injections spaced 2-3 weeks apart. Sometimes more treatments are necessary. It is potentially difficult for cidofovir to penetrate all areas due to scar tissue. This treatment should be reserved for severe cases, with the caveat, severe can be in the eye of the beholder. Histological review demonstrates no evidence of dysplasia. No change in liver function. Typically there is a dramatic initial response. Once the disease does recur, it is typically easier to deal with. It is possible to achieve remission, but certainly not universal for all.
 - c. General Thoughts on Patient Treatment Strategies
 - i. RRP is a variable disease and each patient needs to be approached differently. There are multiple adjunct therapies and no single therapy works in all cases. Patient management requires education of the alternatives, which must include both the pros and cons. It is very important, from the patient perspective, to be aware of misinformation, or chat room and internet chatter. Just because one therapy works on one person doesn’t mean it will work on another.

- ii. RRP requires clear communication with the Physician and Patient. Time needs to be arranged beyond the routine office visit. Prepare the Physician that additional time will be needed to interact, discuss, listen and analyze.
- iii. RRP Plan of action requires frequency of procedure, surgical technique, adjunct therapy and dosing. It also requires flexibility for new approaches if required.
- d. General Questions
 - i. Could remission in cidofovir patients be extended by providing a booster dose at some point in time?
Cidofovir is a powerful mediator and we don't know all of the factors.
 - ii. What happens when Papillomas return after a cidofovir protocol?
Don't know, but generally after cidofovir therapy when/if Papillomas return they are easier to manage.
- e. It is important to remember that there are some very promising therapies that will be available not too far down the road. Thus control of the disease and preservation of the larynx is of critical importance.

Experimental therapies for which the RRPF has very little or no documented patient supplied statistics:
 HPV Vaccines
 Omega-3 Fatty Acids (Fish Oil)
 Cox-2 inhibitors (eg., Celebrex)
 Cimetidine (Tagamet)

Some notes regarding the above chart:

The therapies are documented as follows IFN = interferon, I3C/DIM = indole-3-carbinol (I3C) or Diindolylmethane (DIM), Cidofovir, MumpsVax = mumps/MMR vaccine.

Other therapies with anecdotal reports of efficacy, include: Echinacea and Thuja (homeopathic anti-virals), a mixture of vitamins including vitamin C and vitamin A, ShapeRite immune formula, bleomycin and cobalt. **(These treatments are generally unsubstantiated and some may involve significant side effects. The RRPF makes no recommendation for their usage.)**

Finally, we continue to remind our readers that these results are based on patient perspectives. Although the survey encourages objectivity and quantitative assessment as much as possible, these analyses cannot replace well-designed clinical trials and research. Furthermore, since sample sizes are generally small and no statistical significance tests have been applied to data in the above table, one must interpret these numbers cautiously, especially when considering the natural variability of RRP. However, we do hope that this information can provide some guidance for those patients seeking adjunct therapies as well as those pursuing RRP related research.

I3C/DIM

For background information about the impact of indole-3-carbinol (I3C) / Diindolylmethane (DIM) on estrogen metabolism and how this subsequently may act to reduce the growth rate of respiratory papillomas, see the *RRP Newsletters* Fall 93 through Fall 94 and Fall 97, Winter 2000-01 for **DIM**, as well as Bradlow et al., 1996 *J. of Endocrinology* **150**, S259-S265; Newfield et al., 1993, *Anticancer Research* **13**, 337-342.

How to get I3C or DIM and how much to take

Phytosorb-DIM™ products containing DIM are available from:

BioResponse
 L.L.C. at P.O. Box 288
 Boulder, CO 80306
 Email at etzeligs@bio-response.com
 877-312-5777 or 303-447-3841 - phone; 303-938-8003 - Fax
 Credit card orders (Visa and MasterCard) are being accepted
Internet ordering: You can now order the Phytosorb products on the Internet at www.hormonalbalance.com. If you send an email to support@hormonalbalance.com they will set an account up for you in the Phytosorb group to purchase on the Internet. There are additional discounts available when you order on line. Please let BioResponse know if you are an existing customer. If you are a new customer, please send them your phone number so they can contact you to set up an account.

Phytosorb-DIM is available in two forms:

Adjunct Therapy and Protocol Update

The following reports of statistics and clinical research involving RRP therapies, represents a best effort to make an accurate and objective presentation of information from surveys, articles submitted by investigators, personal communications and reference to literature. Where appropriate, the RRPF has provided its input in a constructive manner, which we hope will best serve the RRP community.

Adjuvant Therapy Survey Update

by Bill Stern

Patient/family assessed impact of some adjuvant therapies reported.

Table 1. Patient/family assessed impact of adjuvant therapies reported.

Therapy	Users	No	Improv	Comp	Partial
I3C/DIM	156	72	84	34	50
DIM †	15	7	8	4	4
IFN	69	29	40	6	34
MMR/Mumps	24	9	15	7	8
Cidofovir	40	8	32	10	22

†The number of users reporting they are using DIM is underestimated because many are not indicating the specific product they are using.

1. Phytosorb-DIM Capsules; 150 mg; 60 capsules per bottle or 75 mg; 90 capsules per bottle.

Estimated dosages; BioResponse recommends that individuals with RRP choose a daily dose which is close to 8 mg/kg/day (see BioResponse article on next page for recent updates on their Phytosorb-DIM product). A typical man weighing 70-85 kg (where kg. = 2.2 lbs.) would take approximately 500 to 700 mg per day. A typical woman weighing 60-70 kg would take from 450 to 600 mg per day.

2. Phytosorb-DIM Flavored* Sprinkles; 9.0 grams per bottle with directions indicating dosage per teaspoon.

At the suggested dosing below, 1 bottle should provide a two-to-four month supply for a child about 50 lbs.

* Available in orange as well as chocolate flavors.

Shipping : US priority mail , UPS, or global priority. Call or e-mail for product pricing

BioResponse has reformulated its "Sprinkles". These new formulations require lesser amounts of the powder to deliver the increased suggested dose. Detailed dosing instructions are included on the bottle label. Guidelines for children are as follows:

Weight in Pounds (lbs)

Amount of Sprinkles in Teaspoons (tsp.) up to 25 lbs. 1/8 tsp 25 to 50 lbs 1/4 tsp, 50 to 75 lbs 3/8 tsp, 75 to 100 lbs 1/2 tsp 100 to 150 lbs 3/4 tsp

(Please consult your doctor, especially for young children.)

Special Note: Unlike I3C, Phytosorb-DIM does not require activation by stomach acid. Individuals who use antacids or H2 blockers like Zantac can take Phytosorb-DIM.

For scientific inquiries contact Michael Zeligs, MD at zeligsmd@bio-response.com

I3C may be purchased from:

Theranaturals Inc.

PO. Box 344

Orem UT 84059-0344

e-mail: theranat@fiber.net

(801)224-8893 - Telephone; (801) 226-6064 - Fax

www.theranaturals.com

[Credit card orders may be placed by phone, fax, web or e-mail]

Theranaturals I3C and B3IM product pricing as of Oct 2006 (includes shipping via USPS priority mail within US):

1 bottle - 100 capsules @ 100 mg -\$20

3 bottles - 100 capsules @ 100 mg - \$55

add \$16.00 to above prices for Fed X shipping.

Approximate dosing information is based on preliminary results of Dr. Leon Bradlow's estrogen metabolism studies, as follows:

Estimated dosages - Adults approx. 400 mg, Children (under 50 lbs.) 100 - 200 mg

Additional I3C Notes

The digestive process is **important** to properly break down I3C (see *RRP Newsletter* - Spring 94). In this regard, try to avoid taking antacids and it is probably best to take I3C at mealtime. It has also been suggested that taking ascorbic acid (vitamin C) along with I3C will produce ascorbigen, which some investigators (Preobrazhenskaya, et al., 1993, *Food Chemistry*, 48,48-52) speculate may be an even more important anti-carcinogen than I3C.

If you do not appear to be responding to I3C, you might want to give DIM a try.

Finally, no matter what product one is using the best way to extend the shelf life is to keep them in a cool dark location such as the refrigerator.

I3C/DIM reported side effects:

- Occasional gastro-intestinal upset
- A couple of instances of dizziness
- A few anecdotal instances of lowered bone density

Science & Research Activities

Proposed Research/Support activities:

The RRP Foundation is asking the RRP research community to **apply for support of RRP related research projects**. These studies may involve (but are not limited to): **Immunology and RRP, genetics and RRP, RRP quality of life/public health issues and new treatment approaches for RRP (in particular pulmonary RRP)**.

Interested researchers should address inquiries and proposals to:

Bill Stern, Director

P.O. Box 6643

Lawrenceville, NJ 08648-0643

Email: bills@rrpf.org

Voices Unheard: The Social Experience of Illness for Patients, Families, Clinicians and Researchers on the Recurrent Respiratory Papillomatosis Community

Jennifer A. Woo

While recurrent respiratory papillomatosis (RRP) is an unpredictable and devastating disease that compromises the voice and airway, there has been little qualitative social science research exploring the social experience of illness for afflicted individuals and their families. This study employs medical anthropology literature and original ethnographic interview data from over 30 patients, family members, clinicians and researchers across the United States. Findings revealed that RRP patients and families experience significant perceived and enacted stigma, develop numerous mechanisms to accommodate the presence of the disease in their lives, and form strong community support networks. Interview subjects also reported numerous social and political obstacles currently challenging basic science papilloma research. Finally, specific suggestions are made for the continued management of the social experience of RRP.

Genetics of Papilloma-Induced Voice Disturbance

Farrel Buchinsky, M.D., Center for Genomic Sciences

We all know that RRP is caused by HPV 6 or 11. Yet many millions of people are exposed to the two viruses and they do not get RRP. So then what is it about the thousands of people with RRP, that their exposure turns into a disease? Furthermore, why do some people just have a “little brush” with RRP while other suffer a crushingly aggressive course? My colleagues and I at the Center for Genomic Sciences at the Allegheny Singer Research Institute in Pittsburgh looked at the available evidence and decided that there must be a genetic susceptibility to the disease. The Center for Genomic Sciences had state-of-the-art genetic analysis capabilities and the RRP Task Force had access to many patients. Thus a collaboration was formed to enroll patients and their parents in the study to determine the genetic factors that make one susceptible to RRP. In 2003 the National Institute on Deafness and Other Communication Disorders (NIDCD) funded the study. Slowly but surely the number of trios (patient + mother + father) grew albeit not as quickly as was needed. Then in 2005 we obtained approval to recruit patients and their parents directly through the support groups. This was made possible by advances in technology that enabled us to obtain enough DNA from someone swishing mouthwash, spitting it into a tube and mailing it to our center. The enrollment rapidly rose. As of May 2006, 393 people have participated in the study with 157 of those people either having RRP currently or at some time in the past. The other 236 people are parents (and some siblings) of the 157 people with RRP.

The first gene that was investigated was, EVER1 which had been shown to be mutated in a skin disease called Epidermodyplasia Verruciformis (EV). While the rare skin condition is not caused by HPV 6 and 11, it is caused by an unusual susceptibility to HPV 5 and 8. We looked at the DNA of all the patients we had at the time to see if any of them had the mutations that were described for the skin disease. Not one person had the mutation. We concluded that the mutations causing EV was not the cause of susceptibility to RRP. We looked at other aspects of the EVER1 gene apart from the described mutations but found no convincing answers. There are many other genes that we want to explore since we know that the proteins they encode have something to do with the way HPV lives in human cells. However, our focus is on a genome-wide approach. We have already analyzed the first few people on a chip that looks at 6000 different spots in the human genome (collection of all of one’s genetic code). The field of genetic discovery is rapidly advancing. It is now possible to look at not just 6000 spots at a time but to analyze 100,000 or 300,000 or even 500,000 of the 3 billion spots that exist in the human genome. Getting so much information from each person will greatly speed up the process and increases chances of discovering the underlying genetic susceptibility. Statistical techniques have been developed that help us make sense of the overwhelming amount of data. One thing is clear though; in order to take advantage of the science and technology the number of enrollees needs to increase a lot (more than double) and must do so in the near future. We need to make the most of the opportunity that the NIDCD has afforded.

A big “Thank You” is due to the 393 people who have participated so far and another big “Thank You” to the NIDCD and for funding the study.

When we have a greater understanding of this disease we will hopefully be able to offer better management of RRP.

For more information please look at the flier that accompanies the newsletter or visit www.rppgenetics.org or e-

mail info@rppgenetics.org or call the Center for Genomic Sciences at (888) 887-7729 and from outside the United States call + 1 (412) 359-4707

Research progress at LIJ Medical Center

Bettie Steinberg, PhD, Long Island Jewish Med. Ctr. Dept. of Otolaryngology

The physicians at LIJ are continuing to enroll patients in their study of celecoxib as an adjunct therapy for moderate to severe RRP (3 or more surgeries in the past year, or tracheal or pulmonary disease). It is a controlled study, with the patients randomized to the drug for one year, followed by a year on placebo, or placebo for one year followed by drug for a year. The investigators do not know whether the patients are taking the drug or the placebo at any given time. Several patients have shown marked improvement in papilloma growth, and one is in remission. However, because of the design, we cannot say until the end of the study whether this is due to the drug. Patients who are interested in participating should contact Dr. Allan Abramson, 718-470-7553, or Ginny Mullooly, RN at 718-470-7011. (For more details, see Spring 05 RRP Newsletter issue).

We are continuing to study the role of the immune system in controlling HPV infections. We have found that white blood cells from patients with RRP react to viral proteins by making a group of signaling molecules (called cytokines) that suppress an effective immune response. There is a strong correlation between the level of these cytokines and the severity of disease. We have also found that there is a correlation between production of these suppressive cytokines and certain variations in genes that regulate the immune response. Taken together, these studies suggest that there may be a genetic susceptibility to either having RRP following airway infection with HPV, or to the severity of the disease. This could help explain why one person has severe disease, while another has mild disease, or why most people with airway HPV infections (5% of the population) have no problem while one person in 30,000 has RRP.

HPV Vaccine Update – 2006

[The following article is being reprinted, nearly in its entirety, with the kind permission of Maney Publishing. It first appeared in the November 2005 Paillomavirus Report- Vol. 16 no. 6. Since its original publication the Merck HPV vaccine has been approved by the FDA, which should provide impetus for pursuing a number of proposed studies discussed in this article.]

Recurrent respiratory papillomatosis:

bright prospects for vaccine-based prevention

Keerti V. Shah¹, Elizabeth R. Unger², Craig S. Derkay³, Bettie M. Steinberg⁴

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Key features of JORRP

The estimates of the annual number of JORRP cases in the US, extrapolated from data from questionnaires (1,4) and from a small population-based study (5) are imprecise and have varied from a low of 80 to a high of 2300 cases. The number of reported cases of JORRP in one survey, without extrapolation, was 840 for the year 1976 (4). Among congenital and perinatal infectious diseases in the US, the number of JORRP cases is similar to that of neonatal herpes (463–2809 cases) and far exceeds the number of cases of rubella syndrome (9 cases), gonococcal ophthalmia (45 cases) and HIV infection (175 cases) (6). Maternal condyloma during pregnancy has been identified consistently as the overwhelming risk factor for JORRP. This association was first suggested in 1956 in a case report (7) and then confirmed in subsequent clinical studies (4,8,9). About 50% of mothers of children with JORRP in these studies give a history of genital warts during pregnancy. A population-based estimate of the magnitude of the relative risk of maternal condyloma for JORRP was made by Silverberg *et al.* (10) for Denmark. They used data from Danish registries over a 20-year period to identify children who were born with a maternal history of genital warts during pregnancy, and reviewed medical records from all ear, nose and throat departments in Danish hospitals to identify cases of JORRP. In this study, which was relatively free of recall bias because it used data previously recorded in national registries, maternal condyloma during pregnancy increased the risk of JORRP in the child by more than 200-fold. However, the risk of JORRP for a child born to a mother who had condyloma in pregnancy was quite low, and estimated to be less than 1%. Maternal condyloma accounted for 37% of the cases identified in the country. Thus, a majority of the JORRP cases apparently resulted from clinically unrecognised HPV-6 and HPV-11 infections

in the mother.

In the genital tract, HPV-6 infections are more frequent than HPV-11 infections but HPV-11 infections account for a majority of JORRP, suggesting that HPV-11 is transmitted more readily from mother to child than HPV-6. Also, HPV-11 is associated with more severe disease (11) as well as with a greater likelihood of malignant conversion (12). In the child with JORRP, HPV is maintained as a latent, subclinical infection throughout the respiratory tract, and is readily recovered from clinically normal mucosal tissues (13–15). Prevention of recurrent disease has been difficult.

Treatments are directed at maintaining the airway rather than elimination of disease. Success is measured as an increase in the time interval between surgeries. Many new treatment modalities are being explored for JORRP as adjuvants to surgery. Treatments currently in use or under evaluation include indole-3-carbinol, intra-lesional mumps vaccine, cidofovir injections, interferon therapy, celecoxib therapy and a potentially therapeutic HspE7 vaccine.

Is caesarean delivery protective?

The generally accepted intra-partum nature of the transmission raised the possibility that JORRP might be prevented by caesarean delivery of the at-risk child. Caesarean delivery is recommended to protect the newborn from neonatal herpes virus infection when the mother has genital herpes lesions at the time of delivery. However, it has not been possible to obtain direct evidence to evaluate this possibility for JORRP because the disease is rare, the frequency of occurrence of JORRP even in the highest-risk group (mothers with condyloma during pregnancy) is low, and many years of follow-up would be required to assess the protective effect of a caesarean delivery. As mentioned

Table 1. Indirect estimates of the effectiveness of caesarean delivery for prevention of JORRP

	Number of JORRP cases	Number by caesarean delivery		Effectiveness	P-value
		Observed	Expected		
Shah <i>et al.</i> (16)	109	1	9.7*	90%	0.0007
Kashima <i>et al.</i> (17)	25	1	7.9**	86%	< 0.05
Shah <i>et al.</i> (18)	138	6	27.4*	78%	< 0.0001
Silverberg <i>et al.</i> (10)	57	7	8.9**	21%	NS
		15	53		

*Estimated from national rates.

**Estimated by comparison with control groups.

earlier, most of the JORRP cases have onset of disease in the first 4 years, but cases with onset as late as 14–15 years are still classified as JORRP. Indirect evidence of the effectiveness of caesarean delivery was sought by comparison of observed caesarean delivery rates in mothers of JORRP cases with expected caesarean deliveries based on national caesarean rates or caesarean rates in control groups (Table 1). In three of the four studies listed in Table 1, the numbers of observed caesarean deliveries were significantly fewer than the numbers of expected deliveries and the estimates of the effectiveness of caesarean delivery in reducing JORRP ranged between 78% and 90% (16–18). In the Danish study, however, seven of 56 JORRP cases were born by caesarean delivery (12.5%) as compared to 8.9 expected cases, corresponding to a non-significant 22% reduction associated with caesarean delivery (10). If the analysis in this study was restricted to the group at highest risk (*i.e.* mothers with condyloma during pregnancy), JORRP occurred in 2 of 471 women delivered by caesarean (0.42%) as compared to in 19 of 2559 women (0.74%) delivered vaginally (Silverberg M, unpublished data). This 43% reduction associated with caesarean delivery in the highest risk group was also not statistically significant. The study did not have enough power for making a reliable estimate in this analysis. Caesarean delivery carried out before the rupture of the

membranes should be protective for infections that are acquired intra-partum. Of the 15 JORRP cases born by caesarean delivery in the four studies listed in Table 1, several were delivered prior to the rupture of the membranes, suggesting that there may be other possible routes of transmission. In addition, there are reports in the literature of JORRP (1) or condyloma (19) being present at birth, an indication that sometimes an infant may become infected *in utero* prior to delivery. In summary, caesarean delivery appeared to afford some protection against JORRP, but the data were inconsistent across the different studies.

Options for a woman who has condyloma during pregnancy

JORRP resulting from subclinical HPV-6 or HPV-11 infection in the mother (*i.e.* a majority of the cases) are essentially unpreventable. But even when the mother has the overwhelming risk factor of condyloma during pregnancy, she does not have many satisfactory options for preventing the disease in her child. Treatments for condylomas are seldom fully effective and some of them are not recommended for pregnant women. While a treatment may reduce the numbers and size of condylomas, the viral infection may persist. The mother is often willing to undergo the risks and financial costs associated with caesarean delivery in order to reduce, even to a small and uncertain

extent, the risk of JORRP in her child. However, the obstetrician is generally not supportive of this strategy for a number of reasons, including the low probability that the child will have JORRP, the evidence that caesarean delivery is not fully protective, the risk of surgery to the mother and the goal of health professionals to reduce the number of caesarean deliveries in the US (20,21). Guidelines for Perinatal Care of the American College of Obstetrics and Gynecology (22) state that caesarean section is not recommended solely to protect the neonate from HPV infection.

The situation is also frustrating from the perspective of clinical care. The cause of the disease is known with certainty, the manner of transmission is known for the most part, and the period of exposure during birth is no more than a fraction of an hour to a few hours. Yet, there is no strategy available to prevent the disease.

HPV vaccines will change the landscape

This dismal situation will undergo a dramatic improvement with the anticipated availability of an FDA-approved HPV vaccine in 2006 that can protect not only against HPV infections that cause cervical cancer, but also against HPV-6 and HPV-11 which cause genital warts and RRP. HPV vaccines are based on virus-like particles (VLPs), which consist of the major viral capsid protein (L1) of HPVs expressed by recombinant DNA technology in yeast or in baculovirus cultures. The expressed L1 protein self-assembles into a VLP which is not infectious (because it does not contain the viral DNA) but is conformationally very similar to the authentic virion. Parenteral immunisation with VLPs results in an antibody response in humans which is 10–100-fold greater than that after natural infection. Antibody titres do decline with time. For previously uninfected women, the vaccines provide virtually 100% protection against incident persistent infections with the viral types included in the vaccine (23–25). The vaccines may also provide some cross-protection against related types which are not included in the vaccine.

Two HPV vaccines are expected to be commercially available in the near future. The Merck vaccine (24), which is expected to be the first to come on the market in 2006, is quadrivalent and contains VLPs not only of HPV-16 and HPV-18, the types which are responsible for a large majority of cervical cancers, but also of HPV-6 and HPV-11, the types responsible for most of genital warts and virtually all cases of JORRP and AORRP. In a recent phase 2, randomised, double-blind, placebo-controlled efficacy trial of this vaccine in over 500 young women monitored for 36 months, HPV-6 and HPV-11 infections or associated disease were encountered 16 times in the placebo group but 0 times in the vaccinated group (24). The second vaccine, from GlaxoSmithKline (25), is a bivalent vaccine and contains only HPV-16 and HPV-18 VLPs; this is expected to be available in Europe a few months after the Merck vaccine.

Both vaccines are expected to reduce the incidence of cervical cancer and cervical cancer precursors, but the quadrivalent vaccine has the additional potential of having a profound effect in reducing the burden of genital warts and of AORRP and JORRP. It is estimated that there are almost one million annual visits to private physicians for genital warts in the US (26). The Advisory Committee on Immunization Practices (ACIP) will develop recommendations

for vaccination only after the vaccine has FDA approval. Merck is developing the vaccine for both men and women and will provide data on immunogenicity in both sexes, although the efficacy of prevention of infections and disease in men will not have been addressed in the first FDA application. If the Merck vaccine gains wide acceptance, it will decrease the circulation of HPV-6 and HPV-11 in the community and will decrease the chance of a woman having condylomas during pregnancy.

Vaccine for young women

In the clinical trials, the vaccines have been shown to be effective in women, aged 16–26 years, who have not been previously infected with the corresponding viruses (23–25). Such women receiving the Merck vaccine will be protected against condyloma as well as against subclinical infections with HPV-6 and HPV-11, so their risk of having a child with JORRP should be reduced to virtually zero.

Vaccine for older women

While discussion about target groups for vaccination have focused on young women before they become sexually active, a large majority of older women in their reproductive years are also likely to have been not infected with HPV-6 and HPV-11. Serological studies of a representative sample of the US population suggest that only 6.3% of 30–39-year-old women have been previously infected with HPV-11 (27), as compared to 17.8% previously infected with HPV-16 (28). In Finland, the prevalence of antibodies to HPV-6 and HPV-11 in 23–31-year-old women in the 1980s and 1990s was 9–12% as compared to 17–24% for HPV-16 (29). The actual number of women previously infected by HPV-6 and HPV-11 is likely to be greater than that suggested by the serological studies because not everyone infected with HPVs mounts a durable immune response. Nevertheless, a majority of adult women have probably not been previously infected with HPV-6 and HPV-11 and could benefit from the vaccine as much as the younger women and, if vaccinated, would also be protected against both genital warts and the risk of having a child with JORRP.

The vaccine may be of benefit even for the woman who has been previously infected with HPV-6 or HPV-11. The vaccine manufacturers have not yet disclosed if the vaccines provide protection against disease to women who are already infected, but the vaccine does boost the immune response in previously infected women. The protection conferred by the vaccine is antibody-mediated; in animal models, serum transferred from an immunised animal to a naïve animal provides protection against tumour formation by challenge with infectious virus (30,31). The child born to a mother who has vaccine-induced high antibody titres against HPV-6 and HPV-11 could be expected to receive large amounts of antibodies transplacentally, and these may help contain the infection and decrease the risk of developing JORRP. In neonatal herpes virus infection, the risk of intra-partum transmission to the child is about 30% if the mother is undergoing a primary HSV infection but 3% if the mother has recurrent HSV infection (32). This markedly decreased risk of HSV transmission is attributed to the lesser severity of recurrent maternal infection and to the high amounts of antibodies transferred to the infant transplacentally (33).

Vaccine for pregnant women with condyloma

In view of the above, it would be worthwhile to consider immunisation of a previously unvaccinated (or vaccinated) pregnant woman with condyloma in order to reduce her risk of having JORRP in the child. The immune response in these women is already primed due to the previous infection and the vaccine will boost it and generate high titres of antibodies which, after transplacental transfer, may provide protection to the newborn.

Vaccine for the newborn

The possibility of post-exposure prophylaxis against JORRP by immunising the newborn with a maternal history of condyloma should also be considered. Such a strategy has been spectacularly successful in protecting infants born to mothers viraemic with hepatitis B virus. A hepatitis B virus vaccine routinely used to immunise newborn infants has provided virtually complete protection against hepatitis B infection (34). With JORRP, there is a time interval of several months to several years between exposure at birth and onset of disease. Immunisation with HPV-6/11 vaccine at birth may, therefore,

be successful in generating immunity prior to the onset of disease and in decreasing the risk of JORRP in the child.

Surveillance of JORRP to evaluate vaccine efficacy

The quadrivalent HPV vaccine is expected to be on the market in the summer of 2006. Depending on the recommended age of vaccination, children born to vaccinated mothers may first appear in 2007. If the vaccine is effective in reducing the risk of JORRP, mothers of children with JORRP will be less likely to have been vaccinated than their age-matched cohort. This could be monitored in 2007 and beyond.

Because of the rarity of the disease, the most efficient way to obtain data needed to evaluate vaccine effectiveness would be to set up national surveillance for newly diagnosed cases of JORRP. Each new case could be investigated to ascertain the diagnosis of JORRP, collect a detailed history of the mother's HPV vaccination and of condyloma during pregnancy, obtain a serum specimen from the mother for HPV-6 and HPV-11 antibody determination, and procure a tissue section from the patient's diagnostic biopsy to identify the HPV type responsible for the JORRP. There is an extensive network of patients who communicate with each other through the web sites of the RRP Foundation (RRPF) and the RRP-ISA Foundation. There is also a network of paediatric otolaryngologists who have already worked together on the Respiratory Papilloma Task Force. Together, these two networks could provide ready access to new patients and collaborating physicians, enhancing the feasibility of the proposed study. The vaccination histories of one or more groups of appropriate control mothers would need to be obtained to estimate the 'expected' number of vaccinated mothers. Assuming the vaccine is 100% effective in preventing infection, if 10% of the control mothers gave a history of vaccination and none of the mothers of JORRP cases were vaccinated, it would require investigation of as few as 35 cases of JORRP to show a statistical difference between expected and observed numbers of immunised mothers. It should be possible to identify and investigate several times that number of JORRP cases in 3–5 years. If immunisation is accepted by a significant fraction of young women, a reliable estimate of the vaccine efficacy could be made by surveillance over a few years. Continuation of surveillance would permit the estimate of duration of protection. Investigation of JORRP cases that may occur despite maternal immunisation will help identify weaknesses in the preventive strategy and ways to improve it.

Conclusions

JORRP can cause life-long disability and is a tremendous burden for the patient and his or her family. The disease is very difficult to treat or to prevent. The anticipated availability of a vaccine which has the potential to prevent this disease greatly brightens the prospects for reducing the burden of JORRP.

Reference list available at:

www.rrpf.org/newletters/RRP_Newsletter_Fall06_Shah_refs.pdf

[The following report is primarily based on phone conversations during the Spring and Summer of 2006 with Mr. Gregory McKee, President and CEO of Nventa Corp. (formerly Stressgen)]

Status of the Nventa (formerly Stressgen) Therapeutic Vaccine for HPV: HspE7

by Bill Stern

The much anticipated Phase III trial of HspE7 for the treatment of RRP will be delayed at least a year. For those with aggressive RRP who have not responded to available therapies, this news is certainly disappointing. However, after recent conversations with Nventa President and CEO, Gregory M. McKee, I am somewhat optimistic that RRP patients can look forward to a new therapeutic option that promises a high degree of efficacy. Nventa/Stressgen apparently spent the last year re-evaluating HspE7 and improving its financial situation. They remain highly committed to the development of a reformulated HspE7 compound that, according to Mr. McKee, has "dramatically increased potency", when compared to the original formulation. This reformulated product has shown some "impressive results" in some pre-clinical case studies involving genital warts. In a more recent press release (also presented at the recent Int. Papillomavirus Meeting), results of a Phase II study of 30 men with anal/genital warts indicated an 81% positive response (after 48 weeks "complete response" in 33% and some improvement in another 48%), the full press release may be viewed at: http://www.nventacorp.com/news/pr20060907_HspE7_warts_data.htm. Mr. McKee is hoping that a Phase II/III clinical trial involving approximately 200 RRP patients might begin near the end of 2007.

In 2005 the original HspE7 product was evaluated for efficacy in treating ~27 RRP patients via a Phase II trial. Results indicated an approximate doubling of surgical intervals on average. With the prospect of a significantly improved HspE7 vaccine product, the RRP community will continue to wait for its availability, hoping for a new therapeutic break through.

More information about Nventa may be found at their website: <http://www.nventacorp.com>

Mucosal vaccines against HPV ?

[as interpreted by Bill Stern]

Nardelli-Haefliger and Revaz (2005, Papillomavirus Report, Vol. 16 no.6) suggest that enhancement of mucosal immunity, rather than systemic immunity, may be more effective against HPV infections. A key aspect of mucosal immunity is the presence of lymphocytes which, when activated, may preferentially migrate in mucosal sites. Furthermore, there exists an immunological network operating on mucosal surfaces that might allow for immunological activity at distal mucosa. Hence, it is speculated that vaccines aerosolized for delivery to mucosa may be more effective than intra-muscular injections. With virtually no trials as yet to test this hypothesis, it is obviously **very speculative and unproven**, but it will be interesting to pursue this approach for future treatment / prevention of HPV/RRP.