Vasoactive Intestinal Polypeptide of VIP is a 28 amino acid long chain peptide secreted in the gut, pancreas and hypothalamus as well as other body tissues with wide ranging effects. VIP was originally isolated from the GI tract from which it derives its name and was noted initially as a potent vasodilator potentiating gut motility and digestion. However, VIP has subsequently been found in the peripheral and central nervous systems and more recently on T-Lymphocytes and likely and important immune regulator and should no longer be considered primarily a gut derived peptide hormone. It has a structure very similar to human growth hormone-releasing hormone (GH-RH) and belongs to the superfamily of glucagon and secretin. It has a half-life of two minutes in the blood but has membrane receptor action through the VIP receptor which is a G Protein-Coupled Receptor (GPCP) that influences the cells at the level of gene transcription like many other potent peptide hormones for much longer periods of time. Note that VIP helps determine day-night diurnal cycling or chronobiology and if that cycle is disturbed, strongly suggests VIP deficiency and sleep disturbance will follow. Diurnal cycling is also important to the oscillating catabolic (daytime) and anabolic (nighttime) metabolic states of normal health.

VIP has had historical effects observed in several tissues:

- In the GI tract VIP induces smooth muscle relaxation (lower esophageal sphincter, stomach and gallbladder), stimulates secretion of water into pancreatic juice and bile and causes inhibition of gastric acid secretion and absorption from the intestinal lumen. Its role in the intestine is to greatly stimulate secretion of water and electrolytes, as well as stimulating pancreatic bicarbonate secretion and inhibiting gastrin-stimulated gastric acid secretion. These effects work together to increase gut motility.
- VIP has the function of stimulating pepsinogen secretion by chief cells in the stomach lining thereby enhancing protein digestion.
- VIP is found in the brain and some autonomic nerves. One region of the brain where VIP strongly localizes includes a specific area of the suprachiasmatic nuclei (SCN) and the location of the ‘master circadian pacemaker’. The SCN coordinates daily timekeeping in the body and VIP plays a key role in communication between individual brain cells within the region. Further, VIP is also involved in synchronizing the timing of the SCN function with the environmental light-dark cycle. Combined, these roles in the SCN make VIP a crucial component of the mammalian circadian timekeeping machinery.
- VIP is found in the heart and has significant effects on the cardiovascular system. It causes coronary artery vasodilation as well as having a positive inotropic and chronotropic effect. Research is being performed to see if it may have a beneficial role in the treatment of heart failure.
- The growth-hormone-releasing hormone (GH-RH) is a member of the VIP family and VIP likely stimulates Growth Hormone secretion in the anterior pituitary gland.
The VIP receptor is localized to even more tissues and is a G protein-coupled receptor that we think is also stimulated by CSF’s including MTF, Anabolic and Catabolic pastes the we have used for years in this clinic. There are two known receptors for the vasoactive intestinal peptide (VIP) termed VPAC1 and VPAC2. Both receptors are members of the 7 transmembrane G protein coupled receptor family.

VPAC1* is distributed widely in the CNS, liver, lung, intestine and T-lymphocytes.
VPAC2* is found in the CNS, pancreas, skeletal muscle, heart, kidney, adipose tissue, testis and stomach.

Rationale or VIP use in CFS patients:
Ritchie Shoemaker, MD in Pocomoke City near Eastern Shore of Maryland (now medically retired)
has recently published a paper2* on 20 patients with a CFS-like illness he calls Chronic Inflammatory Response Syndrome or CIRS that is not distinguishable on clinical grounds from CFS except that Dr. Shoemaker has linked CIRS to water damaged buildings (WDB) with mold exposure. He does not recognize CFS and it is not part of his vernacular. He despises the term CFS as ridiculous and non-specific, even as the same may be said of CIRS-WDB. However, we have traded patients over the years and they look very much the same to both of us. Though we sometimes argue over minor details of our differing points of view, I respect Dr. Shoemaker and believe his views have much merit even as we do not think exactly the same way. Dr. Shoemaker sees the world through the eyes of biotoxin exposure, especially mold toxins and certain water-related toxins from dinoflagellates that cause algal blooms known as red tide3*. The Cheney Clinic sees the world though the eyes of cellular energy production 4,5,6* and redox buffer problems 7,8,9,10*. It turns out that these two points of view can lead to the same place and that is how I view our current scientific relationship.

Dr. Shoemaker’s paper is very interesting from the point of view of CFS-like patient tolerance to Nasal VIP as well as the apparent enduring clinical benefit and their improvement on many hormonal and immunological tests over the 18 months of his study. However, he ended up eliminating a whole group of patients for various reasons so the actual response rate is hidden in his study. What especially interests me is the Pulmonary Artery Systolic Pressure or PASP testing which greatly improved on VIP therapy and could have profound implications in regards to Chronic Hepatic Venous Insufficiency (CHVI) and Chronic Cerebral-Spinal Venous Insufficiency (CCSVI) 11* which we have recently linked to CFS (N > 20)12*.

I have talked to the pharmacy in Massachusetts which produce VIP de novo and they will sell it only to patients on a protocol. It cost approximately $200 per bottle which can last onto four months depending on dosage. That protocol does not have to be Ritchie Shoemaker’s protocol but can be The Cheney Clinic protocol. VIP has special orphan drug status for use in treating pulmonary artery hypertension 13* and can therefore be used on a prospective clinical study for a specified reason that makes clinical sense. Reduction of the pulmonary pressure or PASP as observed by Shoemaker et al2* is exactly what I want to see in a drug that may help eliminate
CHVI and CCSVI. That VIP may also help dysregulated immune14,15* and hormone systems 2* as a neuroregulatory peptide as well as help sleep1* is a significant bonus and its relationship to growth hormone and the ability of anabolic hormones to improve redox buffer is also not lost on me in respect to the potential utility of VIP in CFS.

**Qualify Tests:**
This study will require pre-testing in order to qualify for this study and in addition, with willingness to do pre- and post-testing as described below. Patients with financial, medical or logistical restraints should not participate in this study. Patients not seen in the Cheney Clinic in the past year are not eligible as they are no longer formal patients of the Cheney Clinic according to past policies. Patient with a history of pancreatitis or cholecystitis may not want to participate in this study (see below) though they are not excluded.

All patients must have either CHVI or CCSVI documented and demonstrate some evidence of a positive Nasal VIP response such as a reduction in TrmaxPG or a reduction of CHVI or CCSVI by Doppler ultrasound criteria either here in Asheville or at CCSVI facilities in Atlanta, GA or Newport Beach, CA.

**Pre- and Post-Testing for Nasal VIP therapy in CFS patients:**

**Required Pre-and Post Testing:**

**Physiologic Testing:**
- Echo testing for CHVI or CCSVI both pre- and 6 months to 12 months post-therapy
- Echo testing for Nasal VIP improvement of CHVI of CCSVI criteria pre-therapy
- On-line Visual Contrast Sensitivity (VCS) testing at [http://www.contrastsensitivity.net/cstvs2.html](http://www.contrastsensitivity.net/cstvs2.html) as well as post-therapy(ies)

**Basic Testing:**
- Comprehensive Chemistry Panel
- CBC with differential
- Lipase
- CRP-HS
- Sed rate

**Hormone Testing:**
- Estradiol
- Free and Total Testosterone
- TSH and Free T4
- VIP
- MSH
- 25 hydroxyvitamin-D
- 1-25 dihydroxyvitamin-D
- ADH-Osmolality in AM after non-strict overnight water fast
Immune Testing:
TGF beta-1
MMP-9
Nagalase (HDRI Labs in NJ)
C4a (Only Quest Labs)

Fibrin Deposition and Thrombosis Potential (ISAC):
Soluble Fibrin Monomer
Fibrinogen
PAI-1

Anabolic Metabolism:
NADHP (HDRI Labs in NJ)

Optional Tests:
- ERMI test (wood floor wipe of vacuum rug) if suspect mold or VCS (+).
Order testing kits (wood floor wipe of vacuum rug insert) from http://www.mycometrics.com

-Deep nasal culture for coag negative Staph if suspect sinus infection or VCS (+) or if CRP-HS is high. Get culture kit from http://www.dlmlabs.com/contactus.htm [DLM’s Client Services Department at 1-800-582-6248.]

-Consult with Dr. Cheney for other options if VCS (+) such as oral cholestyramine therapy pre-VIP treatment

Other Recommendations:
I would recommend a modified elimination diet to eliminate gluten, non-fermented dairy, corn, high fructose corn syrup and artificial sweeteners. No tap water.

Recommend Krill oil @ two tabs per day and Colavita Olive Oil at 1 tbsp/day. 32-64oz of Spring Water or #2setting of Life Ionizer/filtered water per day
Continue regular CFS regime you are most stable on

Clinical Questionnaires:
Please fill out and fax or email back to the clinic the attached clinical questionnaire every three months on Nasal VIP up to 12 months or three questionnaires total.

Potential Risks of VIP:
While VIP was well tolerated by twenty CFS-like patients in the Shoemaker study over 18 months, there were notable non-responses in certain subsets of patients and a few clinical setbacks likely related to VIP side effects. There are also some theoretical concerns I have regarding VIP.
The non-responders were most likely to have come from those with continued exposure to mold or other environmental toxins and suggested by a positive VCS test and/or a positive nasal culture for biofilm form coag negative staph which produces a biotoxin that goes right into the hypothalamus. Those with an elevated VEGF and/or elevated MMP-9 indicating tissue hypoxia or chronic inflammation were less likely to respond to VIP. Those left untreated for Diabetes Insipidus with DDAVP were less likely to respond to nasal VIP although the two conditions (low VIP and low ADH) may be connected.

Dr. Shoemaker reported two cases out of over 500 treated with VIP since 2007 who developed pancreatitis. VIP is known to stimulate pancreatic secretions as well as Gal Bladder secretions. Therefore, pancreatitis as well as cholecystitis may be risk factors in the use of VIP.

Perhaps the biggest concern of all is the possibility that a low VIP is being produced as a compensatory response in my CFS cases. The link of VIP to Growth Hormone-Releasing Hormone (GR-RH) is suggestive of this potential link. In 2000, we saw significant improvement with very low dose, sub-sub-physiologic dosed of hGH in CFS but when we approached even sub-physiologic doses of gGH, we saw significant problems in CFS cases including polyarticular arthritis and what we would now term a cytokine storm and clinical decline. After these studies, we took away the idea that the body wanted to down-regulate anabolic tone perhaps to reduce metabolic demand in the face of a low energy state and I can see where low VIP might be doing the same. Therefore, there is a chance and especially at the higher doses of VIP that we will see a similar clinical decline in CFS. On the other hand, the benefits of a least a partial return to normal VIP levels as against the risk of steep decline in VIP with its immunologic, hormonal and sleep consequences may be worth the risks associated with an attempt to see if we can get between these two potential VIP states of very low VIP vs. normal VIP.

In order to protect CFS patients from this potential existential risk of a normal VIP level, we recommend that you start VIP at low dose or one qts in one nostril once per day for a week and then advance slowly at one qts in alternating nostrils week after week to a maximum dose of 4 qts per day in alternating nostril (two in each nostril). Then, I would go back down to one qts per day in reverse fashion over four weeks and then decide what dose range produces the best clinical effects and return to that dose for the duration of the study which is twelve months. Do not hesitate to stop or reduce VIP if you sense a problem and talk to Dr. Cheney about your decision.

**Nasal VIP Therapy:**
We recommend that you start nasal VIP [500mcg/ml] at low dose or one qts in one nostril once per day for a week and advance slowly at one qts in alternating nostrils week after week to a maximum dose of 4 qts per day in alternating nostril (Two each nostril per day). Then, I would go back down to one qts per day in a reverse fashion over four weeks and then decide what dose range produces the best clinical effects and return to that dose for the duration of the study which is twelve months. You will fill out a questionnaire every three months times four and fax or email it aback to The Cheney Clinic.
How to Obtain Nasal VIP:
Once we have your signed consent agreeing to the protocol and Dixie has sent out your test scripts and ordered kits sent to you, we will fax to Hopkinton Pharmacy in Hopkinton, MA a signed script for the Nasal VIP and you can call them and arrange for Nasal VIP shipments. All this assumes you have accomplished all the physiologic tests first and have reported to Dixie the results of your on-line VCS test.

[http://www.rxandhealth.com/compounding/for_mds/formulary_information]

References:

1. [Missing References 1-3]
2. 
3. 


9. Kennedy, G et al. “Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms” Free Biol Med 39, 564-9, 2005


12. Cheney, PR, “CFS linked to CHVI and CCSVI” AAEM Meetings, April 17-21, St. Louis, MO (2013)

