

# LYNDONVILLE NEWS

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The Journal Club is a custom I would like to bring to the newsletter. Some of the articles recently published on CFS and related subjects are of great importance and interest to readers. The articles I choose to review in the Lyndonville News are chosen because I like them and feel like discussing them. I may also review some articles, particularly weak psychosomati. If readers have specific preferences of articles they would like to see reviewed, they are welcome to request it, but I would need for them to send me the full text of the article to be reviewed by snail mail - I have to read the fine print. Not all requests can be reviewed.

I would like to start with some articles on orthostatic intolerance. The first, which appears later in this issue, is an article that I believe will revolutionize the study of CFS, even though it is not even on a patient with CFS, and if it proves to be correct, will only apply to a tiny minority of patients with CFS. Intrigued yet?

## **THE LYNDONVILLE JOURNAL**

**David S. Bell**

### **Orthostatic Intolerance**

Orthostatic intolerance is a term used for illnesses, which are characterized by inability to maintain the upright posture. It is a group of illnesses that overlaps with CFS just as fibromyalgia does, and it may give up leads as to the underlying pathology of the illness. The most exciting new leads are happening in the world of orthostatic intolerance.

Because much of the literature on OI may be unfamiliar to the reader, I will try to summarize it. For those interested in more in-depth reading, I would start with the February 1999 issue of the **American Journal of the Medical Sciences**, (Am J Med Sci 1999;317(2)). This issue is devoted to a review of OI, and much of what I will say here is taken from that issue. The parallels with CFS are tremendous, starting with the title of the first article by David Robertson, "The epidemic of orthostatic tachycardia and orthostatic intolerance".

Defined simply, OI is the presence of symptoms due to inadequate cerebral perfusion on assuming

the upright posture. The usual symptoms include fatigue, nausea, light-headedness, heart palpitations, sweating, and sometimes passing out. Many persons with medically proven OI have been assumed to have emotional problems when they don't. Like CFS, there have been many terms in the past to describe this group of disorders, including "asthenia" Sound familiar? It is not known what is the exact relationship between OI and CFS, and up until recently studies in the two areas have followed separate tracts. The one very nice advantage OI has over CFS is that it can be proven and there are well defined subgroups.

Over the past year in our office we have been testing patients with CFS for OI by two methods. One has been a circulating blood volume study, described in the last section of this series, and the second is a test for orthostatic intolerance. This test is easily done in the office and requires only a blood pressure cuff and a good nurse to catch the patient before passing out.

The test is relatively simple. The patient lies comfortably for ten minutes and BP and pulse are taken several times. Then the patient stands quietly (no moving around) with the blood pressure cuff on, and BP and pulse are taken every few minutes. This is a poor man's tilt test, and I would argue that it is more accurate because it reproduces exactly what happens to a patient waiting in the check out line at the supermarket.

A person with CFS nearly always has orthostatic intolerance. They describe the symptom of fatigue (which is not fatigue at all) which is characterized by being relatively OK while walking down the aisle of the supermarket, but being unable to stand in the checkout line. The orthostatic testing describes physiologically why this occurs.

**There are five separate abnormalities than can occur during quiet standing:**

**1. Orthostatic systolic hypotension** where the upper number (systolic) blood pressure drops. The normal person will not drop BP more than 20 mmHg on standing up. One patient I follow with CFS had a normal BP lying down (100/60) but it fell to 60/0 on standing. No wonder she was unable to stand up - a blood pressure that low is really unable to circulate blood to the brain. In any ICU they would panic seeing a BP like that. And she was turned down for disability because she probably was a hypochondriac.

**2. POTS stands for postural orthostatic tachycardia syndrome.** A healthy person will not change their heart rate standing up for an hour. In a person with POTS, the heart rate increases 28 beats per minute (bpm). Some experts say the heart rate should exceed 120 bpm to have POTS. But either way, this increase occurs frequently in CFS. I think the increase in heart rate is linked to the decrease in blood volume. (Orthostatic intolerance has been called Idiopathic hypovolemia in the past)

**3. Orthostatic narrowing of the pulse pressure.** The pulse pressure is the difference between the lower number of the BP from the higher number. For example, a normal person with a BP of 100/60 would have a pulse pressure of 40. It is actually the difference between the upper and lower number of the BP that circulates blood. If the pulse pressure drops below 18, it is abnormal and blood would not circulate in the brain well. We routinely see in our patients with CFS blood pressures of 90/80, thus a pulse pressure of 10. The current record holder is a young woman with CFS whose pulse pressure fell to 6 mmHg before she passed out.

**4. Orthostatic diastolic hypertension.** The lower number of the BP often reflects the systemic resistance, and while standing many persons with OI and CFS will raise their lower BP number (diastolic) in an attempt to push blood up to the brain. Sometimes this is dramatic. One patient being followed with CFS had a low blood volume, about 60% of normal. While lying down, his BP was 140/80. After standing, his BP rose to 210/140 before we made him lie down. His pulse went up to 140 bpm. He felt rotten but refused to sit down by himself.

As an aside, everyone thought he was a fruitcake - a healthy looking man who said he felt poorly and couldn't work. He was denied disability as usual. Yet when we did the test, he was so determined to stand up I was afraid he was going to stroke out and croak. But he was standing with a BP of 210/140 and a pulse of 140 bpm. He is definitely not a wimp.

After the test, we gave him a liter of saline in the office because he didn't look too good and his blood pressure fell to 90/60 after an hour or so. It is important to note that we had measured his volume the day before so we knew he was hypovolemic. Normally you would never give saline to someone with high blood pressure, it just makes it go higher. In the future, orthostatic testing will require being done in an intensive care unit because these numbers are so scary. Now it is ignored, and patients with CFS called fruitcakes!

**5. Orthostatic diastolic hypotension.** This represents a fall in the lower number of the BP, and seems to be the least frequent abnormality in patients with CFS I have tested.

Below is a listing of the abnormalities and the normal values taken from Dr. David Streeten's book *Orthostatic Disorders of the Circulation*. In the next segment I will describe the results in the first twenty new patients I have tested and how it documents disability. This is important as it will directly measure treatment responses with something other than symptom improvement.

Normal sBP: recumbent: 100-142; Standing (4 min) : 94-141; Orthostatic change: -19 to +11

Normal dBP: recumbent: 55-90; Standing : 61-97; Orthostatic change: -9 to +22

Normal P: recumbent: 54-96; Standing : 62-108; Orthostatic change: -6 to +27

Orthostatic systolic hypotension: fall in systolic blood pressure of 20 mmHg or more

Orthostatic diastolic hypotension: fall in diastolic BP of 10 mm Hg or more.

Orthostatic diastolic hypertension: rise in diastolic BP to 98 mm Hg or higher

Orthostatic narrowing of pulse pressure: fall in pulse pressure to 18 mm Hg or lower.

Orthostatic postural tachycardia: increase in heart rate of 28 bpm or to greater than 110 b/min.

**Reference: Streeten DHP. Orthostatic disorders of the circulation. New York: Plenum, 1987:116.**

## **JOURNAL CLUB**

**A literature review by: David S. Bell**

**ARTICLE:** Shannon JR, Flattem NL, Jordan J, Jacob G, Black BK, Biaggioni I, Blakely RD, Robertson D. **Orthostatic Intolerance and tachycardia associated with norepinephrine-transporter deficiency.** N Engl J Med 2000; 342:541-9

**SUMMARY:** In a recent issue of the New England Journal of Medicine, Dr. David Robertson and colleagues described an abnormality in a gene which causes orthostatic intolerance in three members of a family. The primary case was a woman with orthostatic intolerance (OI), characterized by rapid heart rate, difficulty breathing, cognitive difficulties, and fainting spells related to being in the upright position. Her identical twin had similar symptoms, again usually while standing.

Measurements of norepinephrine while lying down and standing up revealed "hyperadrenergic" orthostatic intolerance, meaning that there was an excessing blood level of norepinephrine while standing. Further testing revealed reduced norepinephrine clearance from the blood stream, and impaired increase of blood levels of norepinephrine after administration of tyramine. The authors analyzed the sequences of the norepinephrine-transporter gene and found an abnormality that impaired the function of this gene in the patient and her twin. They hypothesized that this specific genetic abnormality was the cause of the OI and that "Genetic or acquired deficits in norepinephrine inactivation may underlie hyperadrenergic states that lead to orthostatic intolerance."

**DISCUSSION AND OPINION:** I feel that this article is of tremendous importance to persons with CFS. Central to this issue is the relationship between OI and CFS, a subject discussed in another section of the newsletter. However, both illnesses are characterized by disorders of the autonomic nervous system, particularly excessive sympathetic activation in response to stimuli that should not be stressful, such as standing up.

In a paper written in 1988 the symptoms of CFS were compared to cocaine withdrawal which still remains as an excellent model for the illness. Interestingly, cocaine inhibits norepinephrine reuptake, thus acting in a similar manner to the gene deficit described in this paper. It is because of this deficit that patients experience symptoms suggestive of not enough norepinephrine (adrenaline) simultaneously with too much norepinephrine, a paradox, which underlies much of the confusion regarding CFS. It may be that a physiologic mishandling of norepinephrine lies at the root of both conditions.

It should be noted, however, that even if this study proves to be accurate, it is not likely to explain many cases of OI. The authors state that the abnormal gene sequence was not found in 254 other (unrelated) persons with OI. But the paper is of great importance as it is likely to be the explanation in at least two persons with OI. It is a start.

**1. Lehrer JF, Hover LM. Fatigue Syndrome JAMA [Letter] 1988; 259:842-3.**

## LYNDONVILLE NEWS

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### **JOURNAL CLUB**

**David S. Bell**

**Article: Orthostatic intolerance in adolescent chronic fatigue syndrome.** Stewart J, Gewitz MH, Weldon A, Arlievsky N, Li K, Munoz J. Pediatrics 1999; 103:116-121.

**Summary:** The purpose of the study was to establish the relationship between CFS and orthostatic intolerance (OI) in a group of adolescents diagnosed with CFS by the CDC criteria. 26 adolescents with CFS were compared to adolescents evaluated for simple faint and healthy controls using blood pressure and pulse measurements on a tilt table. Only one CFS patient had normal values, the remainder having severe orthostatic symptoms combined with syncope, orthostatic tachycardia, and orthostatic hypotension. 72% of the CFS patients had abnormal physical examination during head up tilt consisting of blue and swollen legs suggestive of excessive venous pooling. The results on this testing showed clear differences between the three groups.

**Discussion and Opinion:** Orthostatic intolerance is clearly becoming an area where objective findings correlate with subjective symptoms in defining an illness that has loosely been termed chronic fatigue syndrome. Perhaps, of greatest importance is that now there exists a possibility that specific subgroups of CFS may be defined, an area that was never very productive when abnormal immunology was used to stratify patients. Most importantly, studies in this area may help define more rational diagnostic criteria for the illness.

Hypotension was defined as >30 mmHG drop in systolic blood pressure, and orthostatic tachycardia was defined as >30 bpm increase in pulse. Systematic analysis of narrowing of pulse pressure was not done in this paper, but I feel that it is possible that further differentiation from normal adolescents and fainters will be possible with this addition. It remains to be seen whether results with the "poor man's tilt" described by Dr. Streeten will be the same, but casual review of about thirty adolescents done in our office shows striking similar results. (This test requires no tilt table and is carried out by monitoring pulse and BP during quiet standing).

Healthy adolescents will faint on tilt table testing, and 23% did so in this study. However the episodes differed from syncope of CFS as the healthy controls had syncope characterized by a decrease in blood pressure and decreased pulse known as vasodepressor or cardioinhibitory syncope. "Fainters" who are otherwise healthy had similar episodes. Of the CFS patients, only one had had a true syncopal event prior to the study, a detail that I would agree with. Most CFS patients will have light-headedness and dizziness on change of position, but rarely lose consciousness.

The importance of this study is great. It is no longer appropriate for anyone to say that there are no objective abnormalities found in adolescents with CFS. 96% of adolescents with the diagnosis of CFS had the symptoms of orthostatic intolerance (fatigue, dizziness, weakness, headache, sweating, nausea and vomiting) combined with observed abnormalities (confusion, loss in tone, syncope, and excessive venous pooling) while demonstrating objective abnormalities in pulse in blood pressure.

## **LYNDONVILLE NEWS**

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### **Orthostatic Testing Procedure**

**David S. Bell**

A number of people have requested the procedure for orthostatic testing that we perform in the office. It takes about 45 minutes and requires a nurse to be constantly present. It is important to note that this test is difficult for some persons with CFS and an opportunity to rest for an hour after the testing is offered. Intravenous saline is helpful to aid recovery.

- 1.** Patients should be tested late morning or early afternoon with no unusual activity prior to testing. Large meals and large volumes of fluid prior to testing should be avoided.
- 2.** Normal medications should be taken the day of the test. Medications, which affect circulating volume, should be stopped at least two weeks prior to testing, as they will affect the results. Examples are Florinef, diuretics, blood pressure medications, large salt loads. Tricyclics and SSRI medications are acceptable if not for research studies.
- 3.** Blood pressure should be taken with manual blood pressure cuff every three to five minutes, along with pulse. If available, a dynamap or other accurate BP device can be used.
- 4.** Step 1. Patient lying down comfortably for 10 minutes. Pulse and BP are recorded at onset, 5 min and 10 min, along with recording of observations of spontaneously reported symptoms.
- 5.** Step 2. Patient stands without moving or leaning on any object for 30 min or as long as tolerated. If patient pre-syncopal, the test is terminated. Right arm is resting on table at mid chest (heart) level with BP cuff in place. Pulse and BP are taken every 5 minutes, and spontaneous symptoms recorded as well as observations (ie, yawning, feet mottled or bluish, etc.). If symptoms become more severe, pulse and BP are taken every 3 minutes.

### **Results:**

Below is a listing of the abnormalities observed and the normal values taken from Dr. David Streeten's book Orthostatic Disorders of the Circulation.

Normal sBP: recumbent: 100-142; Standing (4 min): 94-141; Orthostatic change: -19 to +11  
Normal dBP: recumbent: 55-90; Standing: 61-97; Orthostatic change: -9 to +22  
Normal P: recumbent: 54-96; Standing: 62-108; Orthostatic change: -6 to +27  
Orthostatic systolic hypotension: fall in systolic blood pressure of 20 mmHg or more  
Orthostatic diastolic hypotension: fall in diastolic BP of 10 mm Hg or more.  
Orthostatic diastolic hypertension: rise in diastolic BP to 98 mm Hg or higher  
Orthostatic narrowing of pulse pressure: reduction in pulse pressure to 18 mm Hg or lower.  
Orthostatic postural tachycardia: increase in heart rate of 28 bpm or to greater than 110 b/min.

**Reference: Streeten DHP. Orthostatic disorders of the circulation. New York: Plenum, 1987:116.**

## **THE JOURNAL CLUB**

**David S. Bell**

**Article:** Jordan J, Shannon JR, Black BK, Paranjape SY, Barwise J, Robertson D. **Raised cerebrovascular resistance in idiopathic orthostatic intolerance.** Evidence for sympathetic vasoconstriction. Hypertension. 1998; 32:699-704

**Summary:** Patients with idiopathic orthostatic intolerance express symptoms suggestive of decreased cerebral blood flow despite normal or only minimal drop in systolic blood pressure. Nine patients were evaluated by tilt table for cerebral blood flow velocity and the effects upon this rate by volume loading and medications. Placebo treated patients had cerebral blood flow velocity reduced by nearly one third. Those treated with volume loading with 2 liters of normal saline and alpha receptor agonist drugs improved cerebral blood flow velocity presumably by improving systemic hemodynamics. Blocking alpha receptors also reduced the decrease in cerebral blood flow velocity but at the expense of systemic hemodynamics. It is assumed that volume loading and alpha receptor agonism improve cerebral blood flow by reduction of reflex sympathetic vasoconstriction of the cerebral blood vessels.

**Discussion and Opinion:** It has been my belief that the mechanisms operant in CFS are very similar to those at work in orthostatic intolerance, and that the common denominator - the symptoms of fatigue, cognitive disturbance, and pain - are due to decreased cerebral blood flow. This elegant paper demonstrates a reduction of cerebral blood flow velocity by one third in patients with OI tilted upright. This finding supports the theory that cerebral blood flow is a crucial factor. The changes in cerebral blood flow cannot be appreciated by physical examination, blood pressure or pulse readings.

If, in fact, the symptoms of OI are due to reduced cerebral blood flow. One hypothetical treatment would be to improve cerebral blood flow, either by increasing intravascular volume, or using agents that would dilate blood vessels. The problem is that agents that dilate cerebral blood vessels also dilate the rest of the blood vessels in the body, thus negating the beneficial effect. The trick would be to dilate cerebral blood vessels while maintaining vasoconstriction in the rest of the body, a trick yet to be performed to my knowledge.

As this is really the beginning of the science of assessing oxygen transport to brain tissue, many technical questions remain, among which is the relationship between cerebral blood flow velocity and cerebral blood flow volume. But studies such as this are promising and add to the evidence implying brain circulation as an underlying issue, at least in OI. And if this proves to be true in OI, I will bet the barn that it will also apply in CFS.

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#### **SUBSCRIPTION INFORMATION:**

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## **FROM JEAN'S DESK**

**Jean Pollard**

### **Disability Evaluations in our office**

A majority of my time is spent doing disability paperwork. In our office we see a number of patients for second opinions and assessment of disability. Private insurance companies may say that we are taking advantage of a gullible public and trying to profit from this, but we do not accept that! CFS can be very disabling, and the law permits compensation in situations where illness has prevented substantive work. Very few physicians are knowledgeable about CFS, and unfortunately, we have seen many patients who are genuinely disabled and entitled to the poverty level compensation permitted by law. In the paragraphs that follow, I will outline the approach that we use in evaluating disability. An evaluation which, by the way, could really be done in any physician's office.

#### **1) Statement of Disability.**

The first statement of the report should reflect the overall level of disability. An example is listed below:

\_\_(name)\_\_ is completely and totally disabled due to Chronic Fatigue Syndrome. His/her illness began in \_(date)\_\_ and progressed with activity restriction resulting in disability starting in \_(date)\_\_. His/her present condition is characterized by less than ( \_\_hours) of upright activity daily, moderate to severe symptoms (add most severe symptoms i.e.: cognitive difficulties and widespread pain). Sustained activity of more than (three hours) at one time results in prolonged exacerbation of symptoms. There estimated level of activity is\_\_\_\_% of normal.

#### **2) Diagnosis.**

The second statement should be a complete listing of diagnoses with a clear indication of which, if any, contribute to the disability. As an example, a patient may have the following:

- A) Chronic Fatigue Syndrome - disabling
- B) Borderline Anemia - not contributing to disability
- C) Mild secondary depression - Secondary to #1
- D) Asthma - Under good control
- E) History of Motor Vehicle Accident - not resulting in disability

#### **3) Clarification of the Diagnosis of CFS.**

How the diagnosis of CFS was arrived at should be stated along with clarification of whether the diagnosis would fulfill the current CDC research criteria. If the criteria do not apply, a statement that the physician believes the diagnosis is correct despite not fulfilling research criteria should be included. Also essential is a statement as to the role of emotions in the diagnosis. As an example:

(Name) has the symptom complex of CFS, including activity limiting fatigue, headache, abdominal pain, muscle and joint pain, recurrent sore throat, cognitive disturbances, and minor symptoms of thirst, sensation of fever, and light and odor sensitivities. (Please note, you would fill in your major/minor symptoms which may not correlate with this list). Exclusionary laboratory examination is negative and supportive laboratory evaluations are present as listed. He/she does not fulfill the research criteria of CFS as the symptom complex has been present since childhood and definitive onset date cannot be established. However, despite not being a research candidate, I believe the appropriate clinical diagnosis for (name) is CFS. Despite (name) having intermittent depression. I do not believe that there is any primary psychiatric emotional illness causing these symptoms or disability, rather I feel that the depression is a result of the CFS.

#### **4) Summary of Clinical Evaluation.**

Listing of medical signs present on examination is essential, such as fibromyalgia tenderpoints, pallor, etc. Summary statement at end should include whether physical exam is or is not consistent with the diagnosis of CFS.

#### **5) Summary of Laboratory Evaluation.**

Supportive laboratory evaluation such as orthostatic testing, circulating blood volume determination, immunologic status should be reported along with negative studies. Supportive laboratory evaluation should be referenced to show that it has been noted to occur in CFS. Example:

Orthostatic testing revealed orthostatic tachycardia with an elevation of pulse on quiet standing of 47 beats per minute (1,2).

(1) DeLorenzo F, Hargreaves J, Kakkar VV. Possible relationship between Chronic Fatigue Syndrome and postural tachycardia syndromes. *Clin Auton Res* 1996 6(5): 263-4.

(2) Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. *Am J Med Sci* 1999; 317:88-101.

It has always been our policy to encourage full work despite CFS because of the devastating effect disability can have on family situations, such as: communication, self-esteem, mood and financial resources. Unfortunately, many persons are disabled due to this illness, and if this occurs, financial aid is possible through Social Security Administration or private disability policies. It had always been our hope that patients with CFS would not need disability help because a cure would be quickly found. Well, that has not happened! While there are many efforts underway to find that cure, there are still only minimal treatments available to help in trying to alleviate the symptoms. As stated many times before, not all treatments work for all CFS patients, and no one knows why. This, in and of itself, is one of the most frustrating aspects of our work. Even more unfortunate is that some truly disabled persons have been denied disability status because of the controversies surrounding this horrible illness. It is one thing to be sick and disabled for years on end; however, it is another to be, disabled, homeless and hungry. I hope that you will find the information given above to be of help in your fight for disability, if you so need it.

◆ We have decided to change one of our very strict policies. We have, in the past, never been able to provide a medical review process for patients who are not already in our practice. However, after careful consideration and many hours of hearing very sad stories, we have changed our minds. What we have chosen to provide is the following:

1) A Chart Review for personal reasons to examine the symptoms and laboratory results of your condition with suggestions of exclusionary blood tests and possible symptomatic treatments which you would give to your primary care physician. Because we would not see you for a physical exam, we would need to review all records including laboratory data for the last 5 years of your illness. Also, Dr. Bell would not be able to prescribe any medications for your condition, as this will only be a Chart Review. Dr. Bell would be happy to discuss this chart review by telephone, and would send you a written report of his opinions. There, of course, would be a charge for this review, and these rates are available by calling me at **the office at 716-765-2060**.

2) A second type of review that is available is a Legal Review. This review is specifically designed and acceptable as expert legal testimony in a court involving disability or other legal proceedings. This type of review is much more time consuming and a written report would be produced with emphasis on the specific legal issues involved. Charges for this review are also available by calling me.

For both of these reviews, it would be necessary for you to fill out a questionnaire that we have drawn up for our CFS patients and it would be very helpful to provide a written chronological report of your illness. Should you wish to have a follow-up office visit, this may be possible given the office time restraints. Insurance will NOT be charged for these reviews, but receipts will be given.