by Joan Livingston

(Editor's note, 2008: This article is a report on a lecture by Dr. Bell and was written for the Massachusetts CFIDS/ME & FM Association newsletter *The UDATE* Winter 1997-1998. The report discusses Dr. Bell's and Dr. Streeten's finding of reduced plasma and red blood cell volume in the blood of Chronic Fatigue Syndrome/Chronic Fatigue and Immune Dysfunction Syndrome/Myalgic Encephalopathy (CFS/CFIDS/ME) patients. While Dr. Bell hypothesized at that time that these factors may be a primary cause of CFS/CFIDS/ME, more current research indicates that other physiological systems play a more important role in the causation of CFS/CFIDS/ME. However, many of the findings of Dr. Bell in this article continue to be current in 2008— these findings point to important physiological processes and symptoms found in the illness.)

It may turn out to be more than just a whimsical metaphor. In describing their illness, many Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) patients say they feel as if their life force has been sucked dry by a vampire. This subjective sensation may in fact be explained by a literal, objective ab-normality, according to Dr. David Bell. New, ex-ploratory research by Dr. Bell and his colleagues suggests that a majority of People with CFIDS (PWC) may have "extraordinarily" low circulating blood volume (note: not low blood pressure), and low red blood cell (RBC) mass (similarly, not anemia or other RBC counts routinely measured in basic blood tests).

While circulating blood volume, levels of plasma (the fluid, non-cellular portion of the blood), and RBC mass are rarely tested in the lab work most of us undergo during annual physicals, they are hardly esoteric measures. They can readily be gauged via standard—"not fancy, not controversial"—blood tests that have been in use for decades.

During a recent presentation to members of the Massachusetts CFIDS/ME & FM Association CFIDS, Dr. Bell—a renowned CFIDS/ME clinician and researcher based in Lyndonville, NY—described "striking" blood abnormalities found in the patients he has studied, abnormalities that may go further than -other, earlier documented anomalies in providing a strong theoretical basis for the constellation of symptoms, sensations, and disabilities inherent in CFIDS/ME. Not previously presented in the U.S., Bell's latest findings are scheduled for publication in the January *Jour-nal of Chronic Fatigue Syndrome,* in an article whose -lead author is endocrinologist Dr. David Streeten of Syracuse, N.Y.

Piecing together the quilt—The ramifications of Dr. Bell's theory? They could be far-reaching, encompassing a simple-to-obtain, possible diagnostic marker *(finally !),* a straightforward explanation for the crazy quilt of fluctuating symptoms experienced by patients (ditto!), a definitive end to the debate about whether CFIDS/ME is psychosomatic (ditto!), and—perhaps most meaningful to PWCs—implications for effective treatments to undo the blood abnormalities and hence resolve the panoply of debilitating CFIDS/ME symptoms (ditto, ditto, *ditto!).*

Until recently, Bell said, "Medical care for CFS has been abysmal. The basic underlying problem has been the lack of physiological markers, which has led to theory after theory about

what's generating these symptoms. There's been almost nothing for physicians to work with. If doctors had a single marker like the visual-evoked response in MS, they'd say, 'Yes, I know what this is and what to do about it.' Instead, they've been bewildered by the pattern of CFS symptoms and often don't know how to deal with them."

Dr. Bell further noted that the Centers for Disease Control & Prevention's (CDC) current, -symptom-based diagnostic criteria are highly problematic, causing "horrendous problems in disability claims, and patients being hassled by insurance companies, with a type of discrimination I think is really inexcusable;" the criteria also generate difficulty in diagnosing children, who may present with symptoms different from those of adults.

Reviewing the Key Symptoms

To lay the foundation for his potentially groundbreak-ing theory, Dr. Bell began by outlining what he sees as the four major clusters of symptoms that any viable theory of CFIDS/ME etiology must explain: *fatigue, neurological symptoms, pain, and multiple sensitivities*.

FATIGUE— Dr. Bell's first observation was that "fatigue" is a totally "inappropriate" word to describe the utter exhaustion and weakness experienced by PWCs. In common usage, it connotes a normal person's recovery from abnormal exertion, "like regaining energy after a busy day"—not the characteristic CFIDS/ME experience. He described CFIDS/ME fatigue as including asthenia (weakness), orthostatic intolerance (the inability to stand up or remain upright, rather than fatigue), and *sensations of impending collapse*—for example, a patient may walk out to her mailbox, and then feel so weak that she feels unable to walk back to the house. The latter may be "the most important [CFIDS-specific] of this first group of

symptoms," he said.

Bell noted that, while *post-exertion* fatigue in CFIDS is not readily improved with rest, "Many patients will say that they feel okay if they just lie down all day—that life becomes tolerable with [*consistent*] rest." Standing up or even sitting up, by contrast, can trigger the fatigue, pain, and other symptoms.

Another unusual aspect of CFIDS/ME fatigue is that it often follows a relapsing-and-remitting pattern—not just day to day, but frequently also over the course of a single day. Many patients might be unable to function in the morning and evening, say, but have higher functioning level for a couple of hours during the afternoon, during which they can run errands or do light housework. On the other hand, some patients have a consistently low functioning level all day long, day after day and year after year: "It has always been my feeling that people with few fluctuations have the worst course [prognosis], while those who feel '20 percent' one day and ‘80%' the next have the greatest chance of recovery. This though, has never been formally documented," Dr. Bell noted.

NEUROLOGICAL SYMPTOMS—While many patients have symptoms in virtually every body system, Dr. Bell feels that the combination of fatigue and *the neurological problems, "which are very disruptive," are the principal factors in PWC's inability to work* .
This second category of symptoms includes the cognitive dysfunction—mental exhaustion, an inability to focus, poor short-term memory—as well as balance disturbances, paresthesias, myoclonus, and lightheadedness or dizziness.

PAIN—Often disabling, pain represents the third key CFIDS/ME symptom Dr. Bell said. "It can be of variable intensity, it may or may not parallel the severity of the illness, and it can be literally any place in the body," he observed, adding that many patients seek care from multiple doctors in their quest for relief: -perhaps an Ear/Nose/Throat (ENT) for headaches, a neurologist for the muscle pain, a gastroenterologist for digestive problems. One consistent and suggestive characteristic of the pain is its laterality—painful lymph nodes, muscles, sore throat, etc., that occur on only *one* side of the body. This suggests to Dr. Bell that CFIDS is *a disorder of pain modulation*
—
"clearly a disorder in the brain"
—
rather
than a problem in the affected organ systems.

SENSITIVITIES—The fourth problem category, multiple sensitivities, is extremely consequential in diagnosis, Dr. Bell stated. It is so common that "I feel there's something wrong with any theory [regarding the basis of CFIDS] that doesn't provide an explanation for these." Sixty to 70 percent of PWCs report sensitivities, he estimated—"an extraordinarily high percentage." The sensitivities from which patients suffer are many and motley: to light, noise, odor, alcohol, drugs, temperature, foods.

Current Theories of Pathogenesis:

The "Why" Behind the "What"

After this symptom review, Dr. Bell proceeded to a *theory* review: a look at the most popular current the-ories about the cause and nature of CFIDS/ME, and their strengths and weaknesses in explaining the illness fully.

First Bell addressed the theory of *persistent subclinical infection*. Historically (especially in the early and mid-'80s), this was the most prevalent hy-pothesis; with reactivated Epstein-Barr virus com-monly considered the driving force behind the illness (which was, in fact, called chronic Epstein-Barr syn-drome at that time). Myriad other agents have been proposed since then, with Human Herpes Virus 6 still under active consideration, as well as other herpes -family viruses, a "stealth" virus, a retrovirus, Cox-sackie virus,
Chlamydia
, and more—
many
more, as any issue of
The UPDATE
or
The CFIDS Chronicle
will demonstrate. Bell finds this theory unconvincing, since no single bodily area of infection and no single causative agent has yet been pinpointed, despite more than a decade of research. "This theory may be correct," he said, "but my hunch says otherwise."

Second is a related conjecture that CFIDS/ME results from *agent-induced immune activation* i.e., that some trigger (most likely a virus or bacterium) alters the immune system and keeps it habitually upreg-ulated, with the bulk of CFIDS/ME symptoms stemming from the immune abnormalities rather than the triggering agent. While this remains the most prominent the-ory at present, it suffers from one deficiency also em-bodied in the first: the failure to identify a single infectious or other agent in a majority of PWCs. Moreover—and more significant—says Dr. Bell, "The sickest people should, but don't, have the worst immune-system activation. The immune activation is there, but we haven't been able to explain why, and if it were
closely
linked to the cause [of CFIDS], the severity of the illness should parallel the severity of the immune activation."

(In a humorous aside, Dr. Bell noted that he once subscribed to this theory but no longer believes it's correct: "If anyone here was misfortunate enough to purchase my book *[The Doctor's Guide to Chronic Fatigue Syndrome],*
this theory is the whole second half of the book. I now think it's all wrong and I want to apologize for having wasted your money. ")

Three other theories that Bell quickly dis-patched: *abnormal adrenal function* (it doesn't ac-count for enough of the CFIDS/ME symptomatology);
mi-tochondrial disease
("hard to study and hard to mea-sure"); and the notion that CFIDS/ME is either
psychoso-matic
or a form of
malingering
("an attitude which, fortunately, is beginning to disappear, especially in the last five years").

Having provided his opinion of these theories and their shortcomings, Dr. Bell introduced *his* ne w hypothesis—still in the initial stages and requiring more research, still not an answer for every patient he's studied, but intuitively logical, consistent with a lion's share of the CFIDS/ME symptoms just listed, and quite promising in terms of identifying treatments:
neurocirculaton asthenia.

Neurocirculatory Asthenia: Or, The Vampire Chronicles

"Neurocirculatory asthenia" is a formidable-sounding term for the rather straightforward findings attendant upon Dr. Bell and Dr. Streeten's recent research. In plain English, it connotes *a person's inability*
—
arising from the brain
—
to maintain adequate, normal blood flow to all areas of the body
("one of the most primitive" human survival mechanisms).

Dr. Bell explained it in part by using post-polio syndrome as a model, because that disorder also stems from brain abnormalities (in this case, true brain *injury).* The syndrome is present in 91 percent of polio survivors, and despite the differences, it does entail chronic symptoms similar to those of CFIDS/ME, including fatigue and cognitive dysfunction (including trouble with concentration, memory, and word-finding).

Autopsies performed on people who did survive their infection with polio reveal lesions in the same areas of the brain believed to be affected in CFIDS/ME. "This model is not particularly encouraging in that damage caused to the brain by polio can be -irreversible, which is worrisome. But I think that CFS symptoms are much more likely to be reversible," Bell -said,

because CFIDS/ME symptoms caused by poor blood -flow to the brain can be reversed if normal blood flow is restored.

Tilt Tables, Tests, Trousers

Bell next addressed the well-publicized Johns Hopkins study involving tilt-table testing, which led directly to his current research focus, for several reasons. Among other things, he knew that *his*
patients had trouble maintaining a standing position (orthostatic hypotension). The Johns Hopkins researchers had identified a similar problem—abnormal heart-rate and blood-pressure responses upon changes in body position—but they hypothesized that the cause was neurally mediated hypotension (NMH), reflecting a derangement in the autonomic nervous system (ANS). Other researchers have attempted to substantiate the Johns Hopkins work but with different study methodologies and thus, different findings, so the work has yet to be replicated.

In his Massachusetts CFIDS/ME & FM Association presentation, Bell pointed out that NMH—from which 22 of the hand-picked 23 Hopkins PWCs suffered —is different from CFIDS/ME; also, it would not explain the full constellation of CFIDS/ME symptoms. As a result. Bell doesn't feel that NMH is the mechanism behind CFIDS/ME; just the same those findings led him to go down a similar road, if not the same road, in studying the cause of CFIDS/ME: "I find this was still a very exciting study and perhaps one of the most interesting directions we are pursu-ing."

One problem with the Hopkins study was that, of the participants, only about half responded favorably and dramatically to the anti-NMH drug Florinef and salt (some others improved on

Procardia, a heart medication; others did not respond to any therapy or actually worsened). *"Th e medications sometimes led to a complete resolution of symptoms. This led me to wonder, why did some people respond to the med-ications and other people don't?*
"
Bell asked. As with so many other CFIDS/ME abnormalities—EBV titers, antinuclear antibodies, specific immune abnormalities—there seemed to be vast differences among people who presumably had the same illness.

Falling down—However, because of the potentially substantial ramifications of the NMH find-ings, Drs. Bell and Streeten conducted related research of their own on 19 severely ill patients. They mea-sured variables including blood pressure, blood volume, norepinephrine (a.k.a. adrenaline, the "stress hor-mone"), and cognitive functioning while their study subjects were lying down, sitting up, and standing for as long as they could tolerate (perhaps predictably, some PWCs simply fainted when asked to stand). While not all patients had abnormalities in norepinephrine, some had surprising reactions to changes in body positions: One patient's level "skyrocketed" upon standing and, after five minutes, so too did her pain—simply *st anding up*
stimulated all her CFIDS/ME symptoms. Bell and Streeten had her don "MAST trousers"—military anti-G-force pants that act as a blood-pressure cuff almost from head (upper chest) to toe, forcing blood up to the brain—and "her symptoms vanished immediately."

Pooling blood—While the stress-hormone findings were often provocative, what seemed to be the most meaningful data to emerge from the study concerned plasma volume, RBC mass, and total circulating blood volume. *Most of the patients had "strikingly abnormal" circulating blood volume; 13 of 19 had both low plasma levels and low RBC mass.*
This was true despite normal blood pressure and normal hematocrits (a standard measure, the RBC-to-plasma ratio; it was presumably normal because the low RBC counts were proportionate to the low plasma levels). In addition, the blood that *was*
present tended to pool in the extremities—particularly the legs—leaving even less blood in the brain for normal cerebral function. Based on these dramatic findings, Bell and Streeten are conducting further research in this area. "Low circulating blood volume," said Bell, "is, I think, the mechanism behind this illness."

The study subjects differed moderately in which blood variables were "off" and by how much, but 16 of 19, for example, had low RBC mass—a shortage of the cells that carry oxygen to the brain and elsewhere. *Interestingly, just one subject had a normal, 100% RBC mass: she recovered and went back to work three months after the study.* With this exception, the findings were quite consistent and re-markable. "Essentially," Dr. Bell observed, "all the patients had low circulating blood volume."

Feeling dead—Besides the woman who re-covered, the participants had an average of *70 percent*
of normal circulating blood-volume levels.
Some ac-tually had less than 50 percent of normal. "That's extraordinary. If you're in a car accident and you lose 50 percent of your blood volume, it's fatal," Dr. Bell noted. "You cannot survive such an acute loss of blood."
(This finding puts a new spin on PWCs' common observation that they "feel dead").

Dr. Bell remarked that he'd assumed the aver-age PWC had been tested for everything—"They have medical files this thick"—but that this particular blood testing is non-routine and has simply been over-looked. It is simple to administer and undergo: you have blood drawn, chromium-51 is added to it, the blood is re-injected, and the volumes are tested two hours later. (Because it takes the body six weeks to clear itself of chromium, the test can be performed only that often.)

What else can affect blood volume? "Living at a high altitude, like the Himalayas, but even that

doesn't affect blood volume much." The illness that seems most similar to CFIDS/ME in this respect, said Bell, is Addison's disease (adrenal insufficiency)—and it, too, causes asthenia, but cortisol treatment "makes it go away." (A possibly interesting side note is the CDC's finding, some time back, that PWC's fre-quently have low cortisol levels.)

If Bell and Streeten's theory proves correct, it might put an end to more than symptoms—it should silence the longstanding body-mind debate. "Nobody can say that a half-normal blood volume is psychosomatic," he noted. "Even if you're nuttier than a fruitcake, it will not affect your blood volume."

Linking Findings to Symptoms

Just a glance back at the four symptom clusters enu-merated earlier will demonstrate how well Bell's new research findings account for CFIDS/ME abnormalities: blood pooling in the extremities, low body-wide blood volume, and resulting low blood flow to the brain have obvious implications for fatigue, neurology prob-lems, pain, and sensitivities. (Regarding alcohol intol-erance, for example, just imagine a PWC's blood alco-hol level after two drinks if the patient has 50 to 70 percent of normal blood volume! Likewise, the low volume could spur over-sensitivity to drugs, histamine, etc.). Even *healthy* people, Bell noted, are instructed to lie down after donating blood to the Red Cross, be-cause of the possibility of fainting and lightheadedness resulting from orthostatic hypotension.

Making sense of mish-mosh—Given that some PWCs seemingly suffer only from low plasma levels and others only from low RBC mass, the mixed treat-ment results at Johns Hopkins begin to make sense: "The *only* thing that Florinef affects is blood

volume," Bell noted. Therefore, the 50 percent of Florinef re-sponders may likely have been those with the lowest blood volumes, not with NMH
per se.
Bell noted that one of the Johns Hopkins subjects treated with Florinef went from a pre-medication functioning level of 20 to 40 percent, quickly recovered on Florinef, and then *stayed*
at 100 percent for two full years, even af-ter discontinuing the drug. She later experienced a re-lapse, went back on Florinef, and recovered com-pletely in two weeks (she is now, not surprisingly,
staying
on Florinef!). "Such a rapid recovery is a re-markable finding and clearly not explained by chance but instead by the drug," Bell said.

Bell also spelled out how his findings could explain many of the signs and symptoms that have seemed like a random mish-mosh until now. To name just one: SPECT scans of PWCs frequently show "holes" in the brain; these represent areas of *insufficient blood flow.* (MRI abnormalities, too, could be the result of low blood volume.)

Issues & Answers

One issue that remains unresolved is whether the severity of PWCs' symptoms are blood-volume depen-dent. Another—as with all newly documented abnormalities—is what causes the blood problems in the first place. "What is it that's keeping the volume low? Other body functions seem to be working ag-gressively to get the volume back up." Bell posited two different basic models, based on what is cause (trigger) and what is effect.

If low volume is what precipitates the other symptoms, "blood transfusions could correct the symptoms"; if the low volume is only secondary, an epiphenomenon, correcting it may be far more diffi-cult because the primary trigger will still be active.

Based on the study, Bell posits that there are two (or three, really) distinct groups of PWCs:

1. those with low RBC mass, who seem to have the worst course; and .
2. those with low plasma volume, which is more likely to resolve with Florinef treatment.

(As already noted, most of the patients actually had both deficiencies.)

While PWCs are all too familiar with the Theory-of-the-Month Club, the work done by Dr. Bell and his colleagues should be easy to replicate (or re-fute) and ideally provide some definitive answers about the mechanism behind CFIDS, pointing the way toward meaningful tests and treatments. Finally, said Dr. Bell, "I hope this will help end the discussion about psychiatric causation." We vampire victims hope so, too.

Question-and-Answer Session with Dr. Bell: Ex□cerpts

Q. Could the RBC count be treated, like anemia, with -iron supplements?

A. No. These are totally different ab-normalities; blood volume in anemia is normal, with the RBC count disproportionately low.

Q. For those who can't tolerate it, is there any substi-tute for Florinef, like Prednisone?

A. No. While not a "miracle cure," this drug is unique in its effect on blood volume and ability to hold onto salt. Pred-nisone has only 1/50 th the salt retaining power of Florinef

Q. What about other therapies, given the distinction between low RBC patients and low plasma patients?

A. One other drug under study is Midodrine, an alpha ag-onist. "It has limited usefulness but seems good with the milder cases, and a number of my patients have had a marvelous response to it."

Q. *Can you talk about pregnancy?*

A. It has long been observed that many women PWCs feel better—even "recovered"—during pregnancy, but the reason for this has been un-known. One explanation from the current study could be the rise in blood volume—an average of 33 percent- that occurs during pregnancy.

Q. *Can you talk about Dyspnea (shortness of breath) on exertion?*

A. "Is it a central mechanism or something the lungs are just per-ceiving?" Possibly, when circulating blood volume drops; the brain (oxygen-starved) may "read" this as shortness of breath, when in fact the lungs are not af-fected.

Q. *What about food allergies?*

A. Bell noted that low blood vol-ume could be responsible for PWCs' apparent food al-lergies, "which you can't really prove." He noted that, after you eat, your blood pools in the gut—again, less cerebral blood flow, and "even a very small change can cause pronounced symptoms in the brain." (This, Bell said, "is why people take siestas after lunch in civilized countries." It appears that, among Florinef responders, food allergies "vanish" with the drug ther-apy. There may be other "pseudo allergy attacks" to other substances, because of the high amount of his-tamine in proportion to blood volume.)

Q. *Any relationship to sleep disturbances?*

A. Yes. "Our bodies have only one mechanism to get more blood to the brain, and that's to put out more norepinephrine—which can cause insomnia, tremulousness, the jitters"—the fight-or-flight response.

Q. Why do we drink so much fluid?

A. Many PWCs routinely carry bottles of liquid with them because of constant thirst—or is it the body's attempt to bring blood volume up to normal? Bell noted that drinking fluids will not help ("you'll just pee it out"). But IV treatments of vitamins or other fluids often *do* make people feel better, for a few hours or couple of days—not, presumably, because of the Vitamin C or other "medical" content but sim-ply because of the large quantity of transfused liquid (Just as the fatigue of Addison's disease is controlled with cortisol; people with diabetes—whose first symp-toms are generally thirst and tiredness—find that cor-recting their sugar levels with insulin corrects the thirst as well as the fatigue.)

Other quick points: PWCs may suffer from *tachy-cardia and premature ventricular contractions (PVC)* ("which are normal most of the time"); unlike most healthy people, *PWCs feel* the PVCs in the chest (a new theory has been proposed regarding the role of another heart disorder in CFIDS/ME, subclinical *my-ocarditis)*

Bell has not been following progress on *Ampligen:*

"Since that first study, I guess I'm not so enthusiastic about it as a long-term answer; the pa-tients I know didn't have any benefit from it"... Yes, *Reynaud's phenomenon* (cold and loss of sensation in fingers, toes) does seem to be slightly increased in CFIDS/ME (sounds like another blood-volume-related symptom to us); similarly, Bell believes that notable facial *pallor* is one of the most characteristic signs of CFIDS/ME.