25 Year Follow-up in Chronic Fatigue Syndrome: Rising Incapacity--Dr. Bell

LAST UPDATED: 25 NOVEMBER 2015

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Editors note: On April 16, 2011, Dr. David S. Bell was the keynote speaker at the Massachusetts CFIDS/ME & FM Association's (MassCFIDS) continuing-education lecture series. The event was co-sponsored by the Massachusetts Department of Public Health at the Hinton State Laboratory Institute Auditorium. Dr. Bell, a retired pediatrician from upstate New York with intense curiosity, set out to find answers as to what made his young patients so ill during the cluster outbreak in the late 1980's. Along the way, he became one of the world's leading researchers on ME/CFS and one of only a handful of physicians who have been able to closely follow his patient population for decades. Dr. Bell has authored many research articles as well as leading books on Chronic Fatigue Syndrome.

by Joan Livingston

You've said it thousands of times: "I'm just fine, thanks." Very likely you've said it a few times today without stopping to think to yourself, "The *hell* I am." Part of living with a chronic disorder, after all, is becoming accustomed to feeling unwell.

Just how unwell patients actually are is a complex issue, and was a primary focus of Dr. David Bell's April 2011 presentation to the Massachusetts CFIDS/ME & FM Association. (His lively talk was well-attended, drawing participants from beyond the state's borders.) A national pioneer in treatment as well as research, Dr. Bell shared the results of his most recent study, an investigation of the current status of people who were diagnosed with ME/CFS twenty-five long years ago.

The study was limited to one group of patients—those who fell ill as children in Bell's rural hometown of Lyndonville, NY—but its provocative findings, on many patients' "rising incapacity," may well have implications for other patients.

Looking back at Lyndonville, NY

Dr. Bell previously published a paper on how well his pediatric-onset patients fared after 13 years, vs. the present timeline of 25 years. At the time of the earlier study, he reported that 80% of patients were "doing okay," with the other 20% remaining disabled. That conclusion was misleading, he now says, because the 80/20 figure created the impression that most patients had overcome the illness. "Doing okay," however, was not synonymous with being well.

About half of those in the "okay" group (or 40% of the total) were truly well. The other 40% still had significant symptoms and should therefore have been differentiated from the completely well and the completely disabled. Many thought they were "fine, thanks"; but they had not recovered.

What is recovery?

How recovery should or could be defined—by patients, by doctors, by society—has still not been resolved in ME/CFS, Bell said. "Is recovery the [total] absence of symptoms and a return to [entirely] normal function?" he asked, pointing out that many patients learn to deal with their limitations so well that they may not be perceived as ill.

The 40% of patients who weren't totally better often led what seemed to be normal lives, but "they had to be careful," Bell said. If they worked or exercised particularly hard, they had to allow themselves recovery time; using a common coping technique, they also tailored their calendars to avoid scheduling too many activities back-to-back. They couldn't work all day and then party at night, the way those who had recovered could.

The issue of recovery is multi-layered. There is no gold-standard lab test, as there are with other illnesses, to establish the absence (or presence) of ME/CFS. And people with chronic symptoms inevitably adapt to them; patients who cope effectively may inadvertently mask how ill they are, even to themselves. The problem is deepened by how well most patients look, and complicated further by the way many individuals, particularly medical professionals, continue to dismiss the reality of the illness.

Perception perplexity

Dr. Bell has long criticized doctors who see ME/CFS patients as psychiatric patients, rather than as physically ill. But MDs aren't the only ones with incorrect perceptions.

"For years I've been saying that people with CFIDS/ME aren't 'fruitcakes,'" he said. "But this is the one place where they actually *are* fruitcakes: They tend to be really confused about how sick they are."

The confusion can be profound; if a doctor as experienced as Bell can't define recovery, how can a patient be sure about his or her illness? Bell coined the phrase "*health-identity confusion*" to denote an inaccurate self-image, the result of "year after year after year of no answer."

The story of one Lyndonville patient illustrated the way doctors contribute to patients' confusion. In diagnosing this woman, Dr. Bell referred her to three different specialists for evaluation. "One doctor said she had Hodgkin's, and had only a year to live. The second said she had Multiple Sclerosis, and had only 10 years to live." Bell paused, then delivered the kicker: "The third said she was a complete fruitcake and would never die."

Little wonder, Bell remarked, that many patients will say, "I'm opting out of this system."

The long-term patients

In designing this and the earlier study, Dr. Bell gauged patients' signs and symptoms via an exhaustive list of objective measurements. The variables ranged from general concerns like fatigue to specific problems like headache, muscle pain, and lymph-node abnormalities. He studied physical functions, emotional symptoms, and mental functions (including memory and cognition) for an in-depth portrait of health status.

Patients were also asked, more subjectively, how well they thought they were. Remarkably, even when they knew they were participating in a medical study, many patients with severe symptoms overstated how well they were.

As with the 13-year study, to which this was a follow-up, 20% of the patients studied were fully disabled. (The study concentrated only on those who were still ill, not those who had recovered. "Those who got better stayed better," Bell asserted.)

Dr. Bell once again divided the unrecovered-but-not-disabled patients into two groups: *persistent* or chronic cases, and *remitting* ones. Patients in the first group were not "okay" in any way; they suffered from persistent symptoms, and functioned poorly.

People in the second group—the remitters—continued to experience many symptoms, but functioned well. Those in the control group (healthy individuals used for comparison to the ME/CFS study patients) had no symptoms and had normal functioning levels.

"Health-identity confusion" seemed to plague those in the remitting category. They considered themselves to be in good health, but all still had symptoms and abnormal lab tests indicating that something was physically amiss.

On the symptom scales, the remitting patients' scores fell about half-way between those of controls and those of chronic patients. A healthy person's score on one symptom might be zero (0), e.g., a chronic/persistent person's score might be 10; and a remitter's, in the middle at five.

Activity levels

Given the large list of factors that determine health, which ones were most important in determining whether someone was improving? Dr. Bell felt that the single most useful criterion in gauging overall well-being was how many hours someone spent engaged in *upright activity* each day: "hours of actually doing something, like work, school, or cleaning; not just sitting around, vegging-out watching TV."

Some people with ME/CFS log only one to five hours of cumulative activity a day, he said (those hours generally aren't consecutive; people might be active for only a few minutes at a time).

Healthy people, or controls, averaged 15 hours of daily activity; the remitting patients, about 13, fairly close to the level of "normals."

Upright activity was the best indicator of relative health in the survey; moreover, Dr. Bell felt it was the most reliable indicator of prognosis and recovery.

"When a person says they are getting better," he said, "it means they can do activities they couldn't do before." Although he posed his rhetorical question about how recovery should be defined, in his own practice he considered activity level and symptom severity in judging status and prognosis.

He warned that prognoses generally seemed poorest among those who remained bedridden for two or more years when they first became ill, and those who experienced particularly bad cognitive problems.

"The severity of the illness at onset is very predictive of the course the illness will take," he said. Worse outcomes were also common among patients who had a bout of infectious mononucleosis, separate from their ME/CFS onset.

Going downhill?

The findings of the 13-year and 25-year surveys were similar. With the exception of those who had recovered, however, no one seemed totally okay this time around.

Forty percent (40%) had essentially no symptoms and apparently normal activity, but they were not as well as controls. Among the 20% who remained disabled, many experienced increasing debility over time.

The remaining 40% (the remitters) still had symptoms, but their activity level was close to normal; that sounds like a good outcome, but in fact many ultimately experienced a return of symptoms or an erosion in activity level.

Dr. Bell called this aspect of his analysis "worrisome" (a patient might call it depressing). Many long-term patients not only didn't improve, but actually seemed to worsen over time.

That was true both of the sickest people, who were already disabled, and many who were recovering. "The bottom line is that people who don't fully recover seem to be getting gradually worse, and that makes me nervous," Bell told a nervous audience.

That a person with a chronic illness could grow even more enervated was one disturbing prospect. That many people don't understand how sick they are was another one.

Dr. Bell gave the example of a mother "who thinks staying at home is her choice. She seems to believe she's basically lazy, which she isn't. But by not trying to enter the workforce, she doesn't have to deal with a lot of issues, including the disability question."

Bell said that some people simply denied they had symptoms, and that others chose to think they were hypochondriacs, rather than acknowledging they were sick.

While a good percentage of those in the Lyndonville study did recover for good, the continuing illness and vulnerability of the others raise vexing questions.

Is this group typical of all ME/CFS patients? It's important to keep in mind that these patients may differ from others in many ways beyond the fact that they got ill as kids; they lived in a small, rural town that experienced a local cluster outbreak in the mid-'80s, one whose triggers remain unknown.

Prime of life, rising incapacity

The trend toward "rising incapacity" in this study caused Dr. Bell to ruminate on how the illness could affect people during what should be the best years of their lives—which ME/CFS does already.

"At 40," he said, "you should be at the top of your profession, thinking, 'Life is good.' At 60, you should be able to retire and to travel." Instead, many people in this group who became sick as children remained ill into middle age, with no indication they would enjoy better health as they got older.

Even those who were already disabled faced the prospect of even worse health.

An interesting side note: To complete this research, Dr. Bell contacted patients who had left the Lyndonville area, and his practice, at some point after their diagnosis and early treatment.

"When I called them, I asked, 'Have you told your current doctor that you have this illness?' A lot of them said something like, 'I'm not going to subject myself to *that*!"

This anecdote lent support to Bell's contention that many patients ultimately decide to avoid the health-care system altogether.

Looking forward

In addition to describing the 25-year study, Dr. Bell described early research into XMRV—a retrovirus recently linked to ME/CFS—and has already developed a new model of the illness, with XMRV as cause, to add to the existing library of "Bell disease models."

(Association members who attended earlier Bell lectures will find the new model similar to others describing the symptom cascade characteristic of the disease.) Dr. Bell actually studied the retrovirus family in the 1990s, thinking these were strong candidates for ME/CFS causation.

He described them this way: "Some viruses, like those in the herpes family, are relatively enormous. A retrovirus is a tiny, primitive thing, something more like our own normal 'junk' DNA. Retroviruses come from our distant past, and are inserted into our chromosomes."

Bell has contributed to early investigations of XMRV performed by the National Institutes of Health (NIH), but was cautious in his remarks. "I'm sorry that the subject is so far from resolution that I can't say much. There are all kinds of controversies about the work, like questions about whether the samples being studied have been contaminated in some way. The technical problems with XMRV are enormous, and I'd prefer not to go into detail about that here. These are issues that must be resolved by scientists; the good news is that smart people will figure it out."

XMRV research itself may be mired in controversy, but the basic concept of the virus as a ME/CFS trigger seems to be on firm footing. After Dr. Bell discussed the challenges ahead, MassCFIDS president Dr. Alan Gurwitt took the floor to say, "For too many years, the federal government failed us. The new people at the NIH and the Centers for Disease Control and Prevention (CDC)

seem sincere, and we're hoping to see some real science now."

Oxidative stress

Bell tied the relatively new idea of XMRV to the concept of oxidative stress as another potential cause of ME/CFS. Oxidative stress is the term for bodily damage caused by free radicals (the "evil" molecules implicated in everything from simple infections to cancer and heart attack). Oxidative stress also reduces energy at the cellular level in the mitochondria, or energy factories, whose function is impaired in this illness. Bell described this part of his theory as follows:

1. Oxidative stress causes aging.
2. Patients have high oxidative stress.
3. In patients, oxidative stress from ME/CFS is added to oxidative stress from aging, causing a double-whammy.

The notion of accelerated aging might ring a bell for patients. Bell stated that "Patients will say, 'I feel like I'm 95. My grandmother is 97, and she's more active than I am.' This raises the question: Can you, at age 40, be a really old person?"

Anyone who's watched the labored gait of a 40-year-old patient, or seen one try to carry heavy packages, would answer yes.

Bell noted that XMRV could lead to infection with or without oxidative stress; if oxidative stress was involved, it would cause an increase in cytokines, disrupt the function of mitochondria, and injure natural-killer cells. Because all these phenomena are characteristic of ME/CFS, oxidative stress is a natural suspect in the causation of the disease.

Like other pathogens, XMRV is also a natural candidate, because the illness so often begins with an acute viral onset. "My bias is that this disease has a discrete cause," Bell said. Having seen so many people who were fine one day and sick the next, "I'm very biased about that; something happened that made patients sick," he said. Is it likely that many people have been infected with XMRV, and that some don't know it? Bell thinks it likely. "People are working on this like mad," Bell said, "but at this point they're working quietly."

Other highlights

Dr. Bell's review of the poor condition of some patients was sobering. More positive was the new work on XMRV and the oxidative-stress theory, because these might offer new insight into the illness and lead to more effective treatments.

Dr. Bell also had positive things to say about even the sickest patients. "I'd like to write a book about the incredible accomplishments of those with CFIDS," he said, citing the example of author Laura Hillenbrand; she wrote the best-selling book *Seabiscuit* while housebound (and mostly bed-bound). The acclaim she's received is unusual, but the way she chose to do something constructive, despite her limitations, was not.

“People learn how to treasure their good time and make something of it," Bell said. "They discover something that gives their life meaning."

Coping styles are important

“How people cope with this is unbelievably important," Bell went on. "And coping is an enormous issue in treatment."
He described three general ways in which patients respond to illness:

- denial
- tilting at medical windmills
- what might be called cheerful patience.

Some people simply ignore the fact that they're sick, he said—the patients who deny their symptoms, or chose to believe they're lazy, for example.

Others "run around and try every treatment out there." (Many patients go through a phase of frenetic activity, sampling alternative "treatments du jour" while also consulting doctors in every specialty. Some maintain this schedule indefinitely, while others burn out.)

Finally, Bell said, are the patients who remain patiently "open to treatment, waiting for that time [of a useful therapy] to happen. They've decided not to make themselves or their families miserable" by focusing obsessively on the illness over which they have so little control.

Condition at five years predictive?

Bell was asked about diagnosis, often a painfully long process, as too many Association members can attest. "My experience is that anybody who looks like they have CFIDS/ME at 3 months, will be diagnosable at 6 months."

Once a patient receives a diagnosis, the next logical question—along with what treatment options are available—is, "How long will this thing last?" Bell sees five years as the point at which an individual's prognosis can often be established.

"If someone's condition isn't improving after five years, if things aren't changing, they're probably going to stay there," he said. "If they're really bad off then, their situation will likely become one of those nightmares we've all heard about." Bell has seen patients improve after the five-year mark, but in his practice, dramatic improvements after that point were not common.

While the focus of the talk was on long-term illness, rather than on patients who recovered or improved, Bell spent some time talking about the patients who saw "good results." He said he had not seen anyone recover as a direct result of *physical therapy*, but cautioned that he had trouble differentiating the effects of exercise from recovery in general.

There are many types of physical therapy. Stretching joints may be important for someone who is developing contractures but, Dr. Bell said, stretching "is not going to increase exertion that much. If you're talking about an exercise therapy where you are out and jogging around the block, you have to use common sense."

Patients must judge for themselves how much exercise they can tolerate (if any), watching carefully for post- exertional malaise. Dr. Bell stated that "Sometimes doctors have no way of assessing this based upon a physical exam."

Asked whether he'd seen any other approaches that correlated with better results, he said no. "There are lots of people who eat terribly, don't exercise, and generally don't take care of themselves who get well anyway," he said.

He was talking not about treatments, but about personal lifestyles, which—at least in his experience—just didn't seem to make much difference in recovery rates.

Whether ME/CFS is casually contagious (can be spread through kisses, coughs, or sharing kitchen utensils) is a perennial question. With the introduction of a new virus, XMRV, audience members once again asked about contagion. "My personal belief is that the disease could be casually contagious only in the first six weeks," Bell said, "but you don't tend to see people transmitting it to anybody else. Transmission would be extremely unlikely with XMRV, because of the low viral load."

The future

Also on the topic of XMRV, Dr. Bell suggested the possibility that many people may have been exposed to this virus without

developing symptoms. He mentioned one patient who didn't have ME/CFS, but had suffered through two years with mononucleosis when she was in college; she tested positive for XMRV. He said he wouldn't be surprised if it turned out that some people who were fine at age 20 became symptomatic as they aged, perhaps developing ME/CFS at age 40 or later. This is another subject for future research.

Bell concluded his remarks by saying, "We should be much further along in our understanding of the illness than we are at present." That we are as far along as we are is due in no small part to Dr. Bell’s persistent work in the face of untold challenges.