Bernard Bihari, MD: Low-dose Naltrexone for Normalizing Immune System Function

**Bernard Bihari, MD**, (1931-2010) was the discoverer of the clinical effects of low-dose naltrexone (LDN) in humans. In his groundbreaking clinical trial of patients with HIV/AIDS at Downstate Medical Center in 1985-86, Dr Bihari discovered the significant effectiveness of low-dose naltrexone in protecting the battered immune systems of those who were infected. With that knowledge, he entered private practice in an attempt to counter the then untreatable disease. As Dr Bihari explains below, the immune-system normalizing effect of the drug application he discovered applies to a wide range of autoimmune disorders.

This interview was provided by Dr Bihari's widow, from a videotape discovered after his death. The interview was transcribed and curated by Julia Schopick, author of *Honest Medicine* (http://www.honestmedicine.com) and champion of effective, cost-efficient treatments that are neglected by current practice. *(Altern Ther Health Med. 2013;19(2):56-65.)*

**Dr Bihari:** My medical training started at Harvard Medical School. I graduated in 1957. Then, I trained in internal medicine at one of the Harvard teaching hospitals in Boston, Beth Israel, and then in neurology at Massachusetts General in Boston. Then, I went to the National Institutes of Health for 2 years doing brain physiology—brain research. I did another residency training in psychiatry in New York, at Columbia Presbyterian Medical Center and then, over the following 5 or 6 years, I got very involved in working in drug addiction. By 1974, I was the [New York] City Addiction Commissioner. I ran all the programs that the city funded for addicts. In 1978, the governor and the mayor met, when the governor took over management of the city's addiction programs, because the city was in a budget crisis. Mayor Koch saved about $8 million and I moved to the city health department as a deputy commissioner. I was the only deputy medical commissioner. I basically ran the city health department for about 3 years. Then I moved to King's County Hospital, where I ran a cluster of addiction programs for drug addicts and alcoholics. By the early 1980s, as the acquired immune deficiency syndrome (AIDS) epidemic began, I got very concerned about it. I was seeing large numbers of the heroin addicts I was treating die. I had a couple of friends who died of human immunodeficiency virus (HIV) in the late 1980s. I got very concerned about what I saw as a major epidemic—a worldwide epidemic—coming over time. That is my background, up to the point where I started doing this research.

**QUESTION:** Can you talk about working with methadone?

**Dr Bihari:** My first job with city government [in New York] was running all of the city health department's methadone programs—there were 41—shortly after the methadone system had been put in place. While I was doing that, the mayor, Abe Beame, moved the addiction services agency into the health department, and I took over the management of all the addiction programs: the drug-free and the methadone programs. And I ran both for about 4 years. I was one of the early proponents of methadone and, because of my job in city government, for a couple of years I was a major spokesperson for methadone—which in subsequent years, I had mixed feelings about. Then I became more broadly involved in drug addiction and alcoholism as a public health problem. Then, later, I shifted my energy to AIDS.

**Q:** How did your connection with naltrexone begin?

**Dr Bihari:** In 1984, the National Institute on Drug Abuse finished the development of naltrexone as an adjunct to treating heroin addicts. Its purpose was to block the heroin high with the hope that it would become a very useful treatment for heroin addicts. It works in heroin addicts by blocking the receptors in cells, mostly in the brain in that situation. Heroin uses primarily the pain receptors: those that are involved in pain relief, and relief of fear. It's a designer drug, really. It was designed in the laboratory to block those receptors and prevent heroin from having access to them. So addicts would take 50 mg a day in the morning and couldn't get high for hours. It would take a very large amount of heroin to overcome the high. And when the drug came out, I was interested in trying it. I gave it to about two dozen heroin addicts who had recently stopped using heroin. None of them would stay on it. At the doses involved, it caused anxiety, depression, irritability. They couldn't sleep, and even minor stresses that they could...
handle the day before, they couldn't handle on days that they took naltrexone in the morning. So it was out on the market, and has remained so since, but has been relatively little used.

One of the things I did know from its development, which I had followed closely because I was treating addicts, is that naltrexone, when taken in large doses, would get the body to triple its production of endorphins. Endorphins are the hormones that heroin mimics. They have a number of functions in the body. They relieve pain; they relieve fear. They're the hormones we use when we're teenagers to cope with social situations and other anxiety-producing situations. It's really endorphins that relieve the anxiety.

They also play a major role during acute stress. For example, an animal that is attacked in the jungle—his body responds by pouring out large amounts of endorphins, and in parallel, of cortisone, which is a cortisone-related hormone. The endorphins in that situation not only relieve the pain, so that when the animal gets injured he's not distracted, they relieve the fright. They also shift blood from the whole gastrointestinal tract to the muscles and brain, which need it during a fight. And, most importantly, they boost the immune system so that the immune cells double very quickly and the immune functions all improve with the large amount of endorphins poured out, so that if the animal gets injured, it's much less likely to get infected and there will be better wound healing.

Because of its role in regulating immune function, I got interested in it in the mid-1980s. In 1985, as I saw the AIDS epidemic expanding, I decided to shift my research energies from addiction to AIDS, and in particular, to look for something that might boost immune function. I knew that the immune system was regulated almost entirely by endorphins, and that also the endorphin production was markedly increased by naltrexone. My colleagues and I worked to find some way of using that ability of naltrexone to raise endorphins, but without the downside of naltrexone blocking the endorphins, the purpose being to find a way to raise endorphins to boost immune function. Along the way, we tested endorphin levels in 10 people with AIDS and found they were extremely low—less than 30% of normal. So the hormones that people with AIDS need the most, to have the immune system fight the virus—those hormones are lacking. So, what we did was to do what's called a "dose ranging trial" to find the best dose of the drug to use to raise endorphins without blocking them at the same time.

We measured the endorphin rises with different doses of naltrexone. We got the same rise with 50 mg, 10 mg, 5 mg, and 3 mg. What we were looking for was the smallest dose that could produce a full naltrexone-induced endorphin rise, if taken late at night. The reason the hour is important is that 90% of the endorphins are made in the middle of the night, between 2:00 and 4:00 in the morning. If a small dose of naltrexone is taken in the late evening, generally at bedtime, endorphin production is boosted as much as threefold, 300%. The naltrexone itself is gone in about 3 hours, but the endorphins remain elevated all the next day. So the naltrexone doesn't significantly block the endorphins but does cause them to rise. If someone with low endorphin levels starts taking low dose naltrexone (LDN) every night, their endorphin levels will triple and stay tripled as long as they're taking the drug.

The first thing we did was a placebo-controlled trial in people with AIDS, in which half of the patients got the drug and the other half got a placebo. They didn't know who was getting what. We started a foundation and raised a little less than $1 million to do the trial. The trial took about 9 months. At the end of the trial it was clear that the people on the drug—once we broke the code—were doing much better than the people on the placebo. They had many fewer deaths—many fewer opportunistic infections that are the cause of death for people with AIDS. Their immune system cells, particularly the T-helper cells, which are the ones most damaged by HIV, dropped significantly less in people on the drug than in people on the placebo. And it looked very promising.

In the course of the trial, I got a call from a friend who was experiencing a recurrence of her non-Hodgkin's lymphoma, which had been treated 5 years earlier with chemotherapy, which had produced a remission. Then, 5 years later, while I was doing this trial, she had a recurrence. Her husband had just died of prostate cancer. He had had a lot of chemotherapy, and had been quite ill with it, and she had very negative feelings at that point about chemotherapy. When her oncologist suggested that she get another round of chemotherapy, he also told her that her tumor was much less likely to respond than it did the first time because lymphoma, in particular, tends to mutate against chemotherapy. So the second round of chemotherapy is not as effective as the first. The third is not as effective as the second. She called me
and said, literally, "Do you think that your AIDS drug would help my cancer?" I had just read a paper in which mice had been injected with human lymphoma cells. It was a breed of mouse that does not reject human cells because of its own immune system, and in this study the mice were all given lymphoma cells—human lymphoma—and died. Then a second group of mice were given lymphoma cells and were first given a single dose of an endorphin—a beta-endorphin. Half of the mice, when given lymphoma cells, did not get lymphoma. The other half did, but it grew much more slowly than in the first group. The researcher who did the study speculated that the endorphin that he gave was working on the cancer by directly affecting opioid receptors on the cancer cells, which are the receptors for endorphins, as they are for heroin and morphine-like painkillers.

Q: Just a single dose?

Dr Bihari: Yes, just a single dose, given in the abdomen.

Q: It acts on the system very quickly then?

Dr Bihari: Yes. But that single dose was enough so that when the tumor cells were injected into the mice shortly after that, they didn't take in half the cases. And in those that did, the cancer had been modified enough so that they grew much more slowly—with a single exposure. Since then, there's been a lot of research studying the relationship between endorphins and cancer in laboratory animals and in the test tube. There are a large number of studies, and the studies that involve giving beta-endorphin (the endorphin from the pituitary gland), metenkephalin (an endorphin made in the adrenal gland), and LDN. The LDN works by inducing the body to make more of both endorphins, so they work similarly to the direct injection of endorphins. All three are effective in markedly reducing the number of cancers that take in mice. Or, once the cancer has been injected and has started growing, in producing remission. That's been true of almost every cancer that has been studied in mice—with pancreatic cancer, colon cancer, cancer of the head and neck, lymphoma, Hodgkin's disease and in a wide range of malignancies that have been injected into mice. The person doing the bulk of that research—the investigator doing it—is a PhD who believes that all cancers have opioid receptors. He's gotten responses with all the cancers that he's treated with endorphins or LDN in laboratory animals. The question arose as to whether the effect on cancer was a direct effect of the endorphins on the tumor or worked through the intermediary effect on the immune system, because it's well known in scientific circles that endorphins boost immune function. In order to separate that out, he did two studies in which he grew cancer cells in the test tube, where there is no immune system. One was colon cancer, and the other was pancreatic cancer. And in both settings the cancer was grown in a nutrient solution, and the cancers were growing rapidly. Adding small amounts of metenkephalin, the adrenal endorphin, to a Petri dish, in both cases led to cell-killing in cancer cell death. Both cancers were destroyed by the endorphins. So, in that case, there was no immune system intermediary. That supported his belief that endorphins work by activating the opioid receptors and producing what's called apoptosis, which is the term for programmed cell death, induced in this case by endorphins—primarily cell death that occurs while the cells are dividing. Of course, cancer cells divide much more rapidly than any other cells in the body. Curiously, chemotherapy also works through apoptosis, through a different mechanism—not through the opioid receptors, but mostly on the cell nucleus through other intermediaries. One major difference is that, since chemotherapy works primarily on the DNA of the cell as it's dividing directly, it also works—besides on cancer cells—it works on other cells of the body.

Chemotherapy side effects are all related to effects on the more rapidly growing cells. That's why there's hair loss, and that's why the white blood count drops. Both involve tissues that are growing more rapidly. Nails stop growing during chemotherapy. Metenkephalin or beta-endorphin, by raising endorphins, work in these animal settings, directly on the cancer cell. And since the endorphins are hormones naturally present in the body, they don't have the same side effects. In fact, they basically have none.

One of the factors involved is that all the studies that have been done, that I'm aware of, of endorphin levels in people with cancer, show that endorphin levels are quite low—generally less than 30% of normal, just as they are in people with AIDS. So, the hormone that the body most needs to fight the cancer is lacking. And giving endorphins, or LDN to raise endorphins, serves as a means of restoring normal endorphin levels in people with cancer. And that appears to have the possibility of producing remissions in some cancers—even restoration to relatively normal levels. One of the implications is that one of the causes of cancer may be a drop in endorphin levels. The endorphin levels may first drop, and by dropping, deprive the body of its most important defense against cancer, which is direct cell-killing by endorphins, indirectly depriving the body of another defense against cancer, which is through immune system cells, called killer cells—natural killer cells, what are called CD8, cytotoxic killer cells. Both are low when endorphins are low. Both are enhanced by the presence of normal levels of endorphins, as are all immune functions. So a drop in endorphins would reduce the immune system’s surveillance against cancer and its ability to kill cancer cells as they arise. The lack of endorphins would also deprive the body of the their direct cell-killing effect on cancer cells. There have been some studies that don't completely tie up the answers to these, but raise possibilities and might explain it. A number of studies have shown that cancers frequently arise after periods of grief. For example, the point in life at which the risk of cancer is the greatest is the year after the death of a spouse. The rate of cancer development 12 months after the death of a spouse is the highest of any point in one's lifetime. Also,
cancers are more frequent as people get older, and that’s probably both because of a decline in immune function as you get older and a decline in endorphin levels as you get older. There have also been some studies, not as easy to prove, that suggest that cancer often arises from 1 to 4 years after a period of sustained chronic stress, which eventually lowers endorphins. To the extent that stress plays a role in cancer development, it likely does it through the intermediary of reducing endorphin levels and thereby depriving the body of its defenses against cancer.

Q: We always hear about endorphins as they relate to exercise.

Dr Bihari: That’s a very good way to boost endorphins and boost immune function. There is no question that people who do aerobic exercise—the kind of exercise associated with cardiovascular fitness—have raised endorphins. That’s been demonstrated. One interesting study was carried out in San Francisco in people with AIDS, all of whom were going to gyms. They were divided into two groups—all men: men who went to the gym regularly just for bodybuilding purposes and did relatively little aerobic exercise; and men who went to the gym on a regular basis to do aerobic exercise with much less attention to bodybuilding and weight training. Both groups had AIDS. Both groups started out with the same level of disease progression. Over a 5-year period, the death rate in the group who were going to the gym for bodybuilding was double that in the group who were doing aerobic exercise. The number of opportunistic infections—the serious infections that kill people with AIDS—was much higher. And it wasn’t because of a harmful effect of bodybuilding. It was rather that the aerobic exercise, by raising endorphins, strengthens immune function and thereby helps to sustain the immune system’s ability to fight HIV. That’s the one study I know of that closely ties exercise with better immune defenses against cancer—then blocking them would do the same as depriving one of endorphins, if you block them completely. So it makes sense, theoretically, that high doses would accelerate the development of cancer. Nobody’s tried that, obviously. He tried it accidentally.

Q: Would he have been a prime candidate for the metenkephalin?

Dr Bihari: Metenkephalin might have been useful for him. It wasn’t really available. Theoretically, it’s not available now. It’s at the moment not a licensed drug anywhere in the world. There have been several studies under FDA approval in the past of metenkephalin in people. There were a series of studies of metenkephalin used to treat cancer, each for short periods of time in individual patients. But in each case, there was only enough metenkephalin to treat people for 3 or 4 months—enough to identify that there was some improvement. Then, in 1990, the company that was funding these studies approached me to do a formal trial of metenkephalin as a treatment for AIDS and HIV infection. And I did.

We did a placebo-controlled study of metenkephalin, giving it intravenously three times a week to people with HIV, all of them in the middle range of T cells. They didn’t have an AIDS diagnosis but were just short of it. In the course of the study, people’s immune function improved significantly, and there were no side effects. The only time we had a side effect was on one occasion when the research nurse working with me gave the intravenous infusion too quickly and the patient started sweating and had a slightly rapid heartbeat. We just lay him down, and he was fine in about 10 minutes. That’s the only time it ever produced side effects.

Right now, there’s only one very small study going on with FDA approval of pancreatic cancer by a research group in Hershey, Pennsylvania. So far, they’ve started three people on metenkephalin, giving it once a week in very high doses. I don’t have any idea as to what they’re seeing. But it is the same institution where all the animal studies that I described were done. Clearly, Dr Ian Zagon, the PhD who did the animal studies, arranged for this trial. As a PhD, he can’t run a clinical trial, but two oncologists at his institution (at Penn State, their medical school in Hershey, Pennsylvania) are doing this trial. There are no other trials going on now.
Unfortunately, the company that funded the trial that I did, in people with AIDS, was not willing to continue funding an expanded drug development, although the FDA was quite interested. They actually used the results from the trial I did as a basis for identifying the drug as safe and nontoxic. But it was around the same time that several large drug companies were developing antiviral drugs for HIV, which have since come out and have been quite successful in affecting the course of HIV and AIDS, and I assume that the small drug company involved was not prepared to compete with them at that time. So, at the moment, there is no research at all going on for people with AIDS with metenkephalin. And the only research going on with people with cancer is this study in Hershey, Pennsylvania.

Q: How many people are involved in that study?

Dr Bihari: So far, three. I do not know how many they plan to do. It is being funded by the National Cancer Institute. I believe the amount of money is not on the order of funding that usually is supplied by drug companies that are investing in a drug based on patents and who expect to make a lot of money from it or hope to make a lot of money from it. This small study funded by the National Cancer Institute, which has funded all the research that Dr Zagon has done up to now. So they are interested enough to fund this small trial.

Q: The study you did was to determine the correct low dose. How many people were involved in that? And why was it so expensive?

Dr Bihari: There were 50 patients involved—51 by the time we stopped it. One-third of the patients got a low dose, one-third got a higher dose, and one-third got a placebo of metenkephalin. It was expensive because clinical trials are very expensive. In this case, they involved visits to the research center three times a week with several staff members—myself, another physician, and research nurses. Then [it included] the cost of infusions and the cost of the drug. It involved the data collection and the expense of filling out all the forms and of analyzing the results. Clinical research is extremely expensive. That trial cost about $600,000, with just 50 patients. So a study large enough to demonstrate whether or not metenkephalin would work for AIDS or cancer would cost in the range of $10 million to $20 million. Now that it has been demonstrated as being safe and nontoxic, it would still cost at least $10 million to $20 million to do a large enough number of patients. The expenses of that kind of research are enormous.

Q: You don't really need to do a study since naltrexone is legal, do you?

Dr Bihari: Naltrexone is a licensed drug, so physicians are allowed by the FDA to prescribe any licensed drug for what they call an off-label use. So the drug is approved for one purpose and used for another. Actually, there are a large number of drugs that are used in that fashion. A lot of the drugs cardiologists use, for example, were discovered to work for high blood pressure. Once they were licensed, they were also discovered to work for heart failure and for angina pectoris from coronary artery disease. A cardiologist friend of mine said that about 60% of the prescriptions he writes for heart patients are for off-label uses. In those cases, it’s usually for the same dose. In the case of naltrexone, the dose we're using is 3 mg a day, so it's for a much lower dose. So the off-label use is legal and medically acceptable. That doesn't mean that the drug has been demonstrated to have efficacy or effectiveness for any of the diseases. It would require large trials done under FDA auspices that were large enough to prove statistically that the drug works. In AIDS, it would depend upon the particular trial, but the goal would probably be to markedly reduce the levels of breakthroughs against antiviral drugs—breakthroughs in the virus growth. And in various kinds of cancers the goals of the trials would be survival, regression of cancer, and so on. You would need a large number of patients for each trial for each use. It would probably cost $10 million to $15 million per study. So if you study LDN for several kinds of cancer, each study would cost several million dollars.

Q: Once the study is done, what would you expect to do?

Dr Bihari: Once the study is done, if the trial is large enough to show efficacy or effectiveness and the FDA decides to license it based on such a trial, and that they would play a role in proving the design of, then it would become an officially licensed drug at 3 mg for that particular purpose.

The two researchers with whom I worked to develop LDN were Vincent Ragone and Finvola Drury. Unfortunately they both have died since. I am working with other people now. But they were key to the drug's development.

Q: What did each of them do?

Dr Bihari: We worked together in designing the trials. They were always present at the research center where the studies were done and helped collect the data. Basically, it was the research design that was most important—and the conceptualization.

Q: I am sort of surprised that Vincent died. I thought it kind of kept him going.

Dr Bihari: The one complication of AIDS that naltrexone doesn’t seem to prevent is AIDS dementia. Some of the new antivirals are very helpful for it. They’re now actually using one of the new Alzheimer's drugs, which are quite successful in treating AIDS dementia, called HIV encephalopathy. The naltrexone, which he took as he got sicker, didn't help with his dementia. But he never had problems with opportunistic infections. His T-helper cells, which are the key immune
system cells in the disease, never dropped, but the HIV encephalopathy was not prevented and he eventually died of that.

**Q:** Are they doing tests to determine someone's endorphin level?

**Dr Bihari:** There is no good commercially available test for endorphins. We did, however, hire a laboratory scientist to run endorphin levels for us. There was a kit that the scientists purchased to do each endorphin level. They are quite expensive. We did endorphin levels—10 tests. We did levels the day before starting naltrexone and the next afternoon in 10 people with AIDS. And we did the same test in 10 people who didn't have AIDS to demonstrate whether or not endorphin levels rose, which they did, 2.5- to threefold. The total cost was about $50,000 for just less than 50 blood tests.

**Q:** Do the blood tests have to be done in the middle of the night?

**Dr Bihari:** Actually, the best time to draw the blood would be in the afternoon at the same time every day—draw the blood before starting naltrexone, and then draw the blood 2 or 3 days later at the same time in the afternoon. Ideally, if I had the funds, I would do it in a sizable number of people. I might try to do it in people who aren't doing as well as I'd like to see, to see if they're responding as well as someone else. There might be some small dosage adjustment that I would make. It is clear the dosage range is no less than 1.75 or 2 mg, and no higher than 4.5 or 5 mg. So the range at which it works is between 1.75 and 5 mg. Three mg is a good dose that covers almost everybody.

The longer you block the endorphins, the less time you have for the endorphins to do their job. The effectiveness is reduced because you have a longer period of blockade of the endorphins. So the ideal is to find a dose for each person that maximally increases the endorphins and minimally blocks them. And it is clear that 1.75 to 5 mg is the dosage range. It might be useful, eventually, to do endorphin levels to find where within that range somebody falls. Or alternatively, the way medicine is practiced, we usually give standardized doses of drugs—to give a standardized dose and then, for people who are not responding or not responding as well as we would expect, to measure endorphin levels at different doses to find if there is another dose somewhat higher or somewhat lower that would work better. But the range would be about the same. It is a very small window for dosage.

**Q:** I am confused about the blocking mechanism. I thought that naltrexone stimulated the endorphins.

**Dr Bihari:** It stimulates by blocking. It blocks the receptors for opiates for endorphins in the hypothalamus, the structure in the base of the brain. And when it blocks those, the hypothalamus begins producing larger amounts, in the middle of the night, of a complex prohormone called proopiomelanocortin. That's a hormone that breaks up eventually into three hormones and goes down a small stalk into the pituitary gland. In the pituitary gland, it's broken down by enzymes into beta-endorphin, a hormone called adrenocorticotropic hormone (ACTH), and a melanin-stimulating hormone. So, that we know for sure. It induces the adrenal gland to make more enkephalin through a prohormone called proenkephalin. It causes the increase by blocking. What the blocking does is it gives the body a false message that the body doesn't have enough endorphins, and so the body responds with exquisite sensitivity by making more. This is a foreign substance, and yet, this foreign substance induces the body to make more of a natural substance that's in the body. So it works by blocking. By blocking, it causes an increase in endorphin production. That's why the dose is so critical, because we could just give everybody 50 mg and get an increase, but 50 mg would block the endorphins completely and they wouldn't do any good. So the ideal dose would be the dose that produces a maximal increase but a minimal blockade of endorphins in the periphery.

**Q:** When the endorphins are stimulated in the middle of the night, does that level stay through the day?

**Dr Bihari:** Beta-endorphin, we know does. Beta-endorphin has a very long life in the body. The term that's used with hormones and drugs is half-life, which means how long it takes for half of a substance—a hormone or a drug—for the body to get rid of it—to leave. And the half-life of beta-endorphin is about 20 hours. That means if you raise beta-endorphin levels between 2:00 and 4:00 in the morning, you still have much higher levels all the next day into the next evening. Metenkephalin is harder to measure because when it's produced, unlike beta-endorphin, it immediately goes into cells. It stimulates the opioid receptors and goes inside the cells. The levels that we measure are not as reliable the next day. Presumably the cells of the body contain larger amounts of metenkephalin, but you wouldn't be able to tell easily by doing blood levels. I hope that we can.

Potentially there could be a value in using both together. The naltrexone would get the body to make more endorphins, both beta-endorphin and metenkephalin. Of the two endorphins, those are the two most common endorphins. There are others. There is one called dynorphin, whose functions are less clear, that is present mostly in the testicles. But the two most important ones for enhancing immune function and for killing cancer cells are endorphins that have what are called delta opioid receptor effects.

There are several different kinds of opioid receptors. The mu (m) receptors are the pain receptors—mu named after morphine. Those are in the brain. The delta receptors are the receptors present primarily in small amounts in the brain but present in many tissues in the body—in most tissues. The delta receptors play very little role, if any, in pain relief, but they do play a major role in not only controlling cancer, but...
in many of the effects that I described before that endorphins have. For example, the receptors in the immune-system cells are primarily delta receptors. Most of the peripheral, systemic effects of endorphins are mediated through the delta receptors.

There is actually one endorphin receptor, the kappa receptor, that seems to be the receptor for the drug, phencyclidine (PCP), and is present in the brain. PCP is a hallucinogenic drug, and what the relationship is between that receptor, brain function, and endorphins is very unclear. But there is one opioid receptor that is particularly responsive to PCP.

And there is some evidence that endorphins may play some role in controlling psychosis. I’ve actually seen examples of it—probably involving the PCP receptors, especially when I was treating a lot of methadone patients. When people were slowly taken off methadone, about 3% to 4% became psychotic as the methadone dose was reduced. For those people, there tends to be a critical dose of methadone that prevents the psychosis. When you drop below that dose, it appears. So below a certain dose, generally in the 5 to 20 mg range, people would begin hearing voices, seeing things, having very disturbed thinking, and developing—in some cases—all of the symptoms of schizophrenia. Those are the people who had to stay on the methadone. Now, if methadone in those patients relieved their psychosis, it may well be that methadone has some effects on the receptors—the PCP opioid related receptors. In its absence, those receptors are too active and produce psychotic symptoms. And in its presence they are suppressed. But nobody has done a lot of follow-up research. There has been some interest in investigating that relationship, but not enough, I think, to demonstrate what role endorphins and opioid receptors play in diseases like schizophrenia. They clearly play some role in some patients—people with schizophrenia.

Q: What kind of numbers are there of people who are using naltrexone?

Dr. Bihari: As far as I can tell—mostly by calling pharmacies around the country—there are somewhere between 30,000 and 40,000 people on LDN. From conversations with the pharmacists and with the physicians who are using it a lot, about two-thirds of them are taking it to treat HIV and AIDS, and in particular—more recently—with the purpose of trying to prevent or treat a complication of one of the family of antiviral drugs for HIV called protease inhibitors. It is a complication in which fat metabolism is disturbed and fat redistributes itself so that people’s bodies become very distorted in shape and their blood cholesterol and triglycerides go sky high. There is a disturbance in all aspects of fat metabolism, and naltrexone appears, anecdotally in my practice, to prevent that kind of complication—because not a single patient who I’ve treated with these new drugs, nearly 200, who are also on naltrexone, has gotten that complication. Around the world, about one-third of people on those drugs get the complication within 1 year, so that does strongly suggest that naltrexone prevents it. Also, four of my patients with AIDS, or HIV, who are taking naltrexone with antiviral drugs stopped the naltrexone after starting the new antivirals. And after they saw the dramatic effects of the new antivirals, all four developed this complication, which is called lipodystrophy, generally 7 to 10 months after stopping the naltrexone. All four resumed taking it, after calling me, and two of the four had a complete reversal of this lipodystrophy. A third one has had about a 70% reversal in the first 7 months. And the fourth one has had no more than about a 20% reversal after 1 year. So three out of four have had a good response in terms of clearing up of this complication.

Of 30,000 people, two-thirds are taking it for HIV; others are taking it to treat various kinds of cancer and autoimmune diseases—primarily those three kinds of disease.

Q: How about the autoimmune diseases?

Dr. Bihari: I can only guess, but I’ve seen people with autoimmune diseases who respond to it. What is clear is that the immune system’s harmony and orchestration is disturbed in autoimmune diseases. What tends to happen in a large percentage of autoimmune diseases is that the T-helper cells, which are the ones that are most vulnerable in HIV, are impaired in their function. Their numbers don’t drop substantially, but their function is impaired. They are really the master cells of the immune system. They are the ones that orchestrate the actions of the others. When they are not functioning well, one of the functions of other immune system cells that is very important is lost—that is, the ability the immune system has to distinguish between those chemical structures in the body that are “ME”—that belong to the self—and those that are foreign to the self. It is that ability to distinguish between self and nonself that allows the immune system to recognize bacteria as foreign, and attack them, or [attack] parasites or funguses or cancer cells, which mutate enough so they become foreigners—as foreign, almost, as bacteria or funguses, and become the object of attack by immune system cells. What happens, apparently, in many autoimmune diseases is that some of the immune system cells, in particular cells called macrophages and cytotoxic killer cells, lose the ability to make that distinction, usually with regard to one, or sometimes more than one, system of the body and they start attacking the body’s tissues.

In multiple sclerosis, for example, the killer cells or macrophages start attacking the myelin sheath, which insulates nerve fibers. And it is the attack of the immune system on the nerve fibers that causes the neurological impairments in multiple sclerosis. And there does appear to be significant benefit to using LDN in treating multiple sclerosis in terms of preventing further attacks of progression. And I assume, based on this kind of research, that it is working by enhancing the functioning of the T cells, thereby restoring the proper orchestration of immune function, thereby stopping the attack cells from attacking the insulation of nerve fibers.

But it seems to work quite well in a range of autoim-
Conversations With Bernard Bihari, MD

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endorphin levels causes reversal of the disease process.

Q: It must be frustrating to have this drug and not be able to get it out there.

Dr Bihari: No question. What I am frustrated about is not having the funds to do the proper clinical trials. What I am doing about that is to negotiate with drug companies that show some interest. If I find a drug company that is prepared to do the work involved and put out the funding involved—the drug company would do clinical trials under FDA guidelines for each disease for which the drug appears to be useful. And once the drug was shown to be effective, if it is effective for each disease, the FDA would license it, and then it would become a licensed drug at 3 mg for that particular purpose. But doctors would also be able to start using it—using the 3-mg capsules for other diseases, too, that they would very likely realize are related to the disease for which it's approved. It is very frustrating to me, because from my own experience, it seems to be pretty clear that the drug has a lot of value. But it really doesn't in a formal way, and in a way that will lead other physicians on a large scale to pick up and use it until it's been officially approved by going through this process. That is frustrating. It takes a long time to find the right company to partner with to develop it.

Q: Could there possibly be a benefactor like Bill Gates?

Dr Bihari: Well, he would have the money. I calculated that doing the first three trials would cost about $50 million, but he would then need a company that has the capacity to not only test it, but to work with the FDA, to follow their guidelines, to bring it through the approval process—then to manufacture, distribute it, and advertise it. Only drug companies and biotech companies have that capacity. So, funding could come from outside—venture capitalists, or even people like the Gates, who have set up large foundations. But eventually the money would have to go to a company that has the capacity to take all those steps and do it well.

Q: It seems like, if you got the word out about these 30 000 people that are involved with this, that that would have some effect.

Dr Bihari: Well it is. The word is spreading through the Internet about it, and a lot of people are trying it, and in most cases, they are getting their own physicians to prescribe it. I certainly haven't prescribed it to 30 000 people. I have, perhaps, 800 or 900 at most, right now, whom I'm following on it. So a lot of people are on it through their own physicians. And one of the things that make it easy for physicians to prescribe it, once they read about it and think about it, is that the toxicity is really zero. There is absolutely no toxic effect at all. No side effects on a short-term, or a long-term basis, so there is no downside to it. And it is quite inexpensive. Most pharmacies charge $24 to $25 for a month's supply, so it's not toxic to the pocketbook either.

If a drug company got involved and got it approved at 3 mg, that would become the official form. That would be the dosage and product for which insurance companies would pay. They wouldn't pay for a pharmacist to grind it up and make 3-mg capsules. They would only pay for the officially approved drug manufactured by such-and-such a company. So if it does go through trials, the companies I've talked to all agree that it would not be a major impediment. What probably would happen is that the vast majority of people taking it would take the 3-mg capsules made by the company that owns it through the licensing, and only those people who don't have insurance would have to pay larger amounts for the drug, because the price would certainly go up from the current compounding pharmacy price. For the people who have no insurance, it would be cheaper to have a pharmacist make it up. It won't matter to them, because they are not going to get it paid for one way or the other. That probably would amount to 10% of the people taking it. So, if 90% of the people taking it are taking it in the form in which it has been approved, made by the company for which it's been approved, then the company will make lots of money. That should not be an impediment.

Q: It seems to me that you're in a position where you could avoid the whole FDA involvement.

Dr Bihari: People could avoid it—and do, since it's legal for doctors to give it now. But it's not going to be universally used for any disease until it's licensed. Most physicians are not willing to prescribe it. So, until it's shown in really good, scientifically designed studies to work, only then will it become widely known—widely understood. Only at that point would physicians not only prescribe it as routine for those diseases for which it works, but the follow-up research would be done to identify how it works, what it does, and what other diseases for which it might work. At the moment, it is a sort of haphazard system in which it has not really been proven that it works for anything except at high doses, although it appears to have some benefit at low doses. It really has to be proven in a scientific way. And I understand that, because I am a scientist. I've done sizable numbers of clinical trials and, although I have used other drugs off-label for patients, I would rather give people drugs that have gone through scientific study. But I wouldn't hesitate to give a drug like this in a smaller dose that's already licensed. It's just a
matter that the licensing by the FDA would not only make it immediately available to everybody. It would lead to insurance reimbursement. It would lead to physicians understanding what it is useful for. It would lead to more studies—probably studies to extend its uses for other things that I am not even aware of—if it does turn out to work in these trials.

Q: So right now you're searching for a drug company?

Dr Bihari: Right now, I am looking for a drug company with which to negotiate for the purpose of having the company make a contractual commitment to do clinical trials for HIV and AIDS, at least two or three kinds of cancer, and autoimmune diseases; and to make a commitment to carry each use, if the drug is licensed—if the trials show effectiveness—to develop it for each use. Then, commit to manufacture it and market it and distribute it. To negotiate a contract with me so I can license patents to them so that they would be in a position to make a sizable enough profit to make their investment worthwhile.

Q: What kind of success do you need in a trial?

Dr Bihari: The general standard is that the drug needs to be at least 5% better than a placebo. That's all. A lot of drugs have been approved just for that small difference. And usually the clinical trials are designed with the assumption that it would be 5% better with large enough cases to demonstrate a 5% difference. The drug may well have more than that degree of effectiveness. But the standards really are 5%, particularly in a drug that has little or no toxicity.

But, with the results I'm getting with HIV and AIDS with combining LDN with antiviral drugs—also for people with cancer and autoimmune diseases—it looks anecdotally, from the point of view of a private practitioner, it looks like it's a lot more effective than 5% over placebo—probably in the range of 60% to 70% effective. I would say that LDN has an overall effectiveness of 50% to 70%. That is my impression. Unfortunately, being the developer of this, I don't know how biased I am in my observations, nor does anybody else. So this kind of anecdotal information can't serve as the basis for licensing. It really requires that the trials be done by somebody else in each field for each disease with people who specialize in that disease. I have had experience doing research—clinical trials for that disease. But these trials have to be done by people who have no financial interest, which obviously I do. That would provide much more credibility for the results, which my results lack, because of the nature of the way I'm involved with it.

Q: You're also using it for hepatitis C?

Dr Bihari: Yes, I am. With hepatitis C, it is hard for me to identify how much it does, because I'm using it with purified extract of St John's wort, the plant in which an ingredient called hypericon has been extracted from the St John's wort and added back in about 22-fold. So, since hypericon in the test tube is extremely effective against hepatitis C and hepatitis B, I had a company make this concentrated form up to use in treating people with those two kinds of hepatitis. And the combination of that with LDN looks very promising. It looks to me like the hypericon, the concentrated St John's wort, looks to be the more important of the two ingredients. I think the naltrexone is helpful with any chronic infection, but the more dramatic element here is the hypericon. In the test tube, it really suppresses these two viruses. In people it seems to suppress hepatitis B and hepatitis C growth and markedly improve liver function.

Q: So naltrexone is an all-purpose immune booster.

Dr Bihari: Right. Naltrexone should be useful in treating any chronic infection—tuberculosis, for example; Lyme disease; certainly diseases like genital herpes, which I do have a patent for. It seems to be effective for people infected with genital herpes in preventing recurring attacks. So by boosting immune function, it appears to have benefit in a wide range of infections by increasing the immune system's ability to control them. With hepatitis C, it's hard to separate out what it does, because the hypericon acts as an antiviral.

Q: The more I learn about LDN, the more it seems like it should be like a vitamin.

Dr Bihari: (Laughs) It also could be viewed as a kind of snake oil! That's the concern I have, that when you start talking about a drug that has such a wide range of potential values, sometimes people think you are a snake oil salesman. I'm really not. Each one of the things that I use it for involves diseases I have been treating for a long time. I have collected data as carefully as I can in my practice and it looks very promising for many things.

Q: Do you and your family take it?

Dr Bihari: Yes, I've been taking it for several years, because my grandfather died of colon cancer. My wife takes it because of a very strong family history of breast cancer. We have a number of friends who take it because of family histories of cancer. It seems intuitively obvious to them, as it does to me, that a drug that would effectively treat cancer should also help prevent it. Proving that would be a massive effort. You'd have to follow 50,000 people who are in high risk groups for 5 to 10 years. One of the likely off-label uses once it's approved will be by people who realize intuitively that it works to prevent cancer, and they'll start taking it.

Q: And there is no reason you can think of to NOT take it?

Dr Bihari: There's no downside to it. Of all the people I've given it to ... First of all, with other physicians, if they run
into what they consider side effects, they always call me because my name is so associated with it. The only side effect I have seen is a very small percentage of people find that on 3 mg their sleep is poor. All they need to do is lower the dose. It simply means that the 3-mg dose is too high for them because they are more sensitive to it. Generally lowering it to 2 mg is enough—lowering to 2 mg or 1.5 mg is enough to eliminate the sleep disturbance. That is literally the only side effect that I’ve seen. I’ve had two women on it for 14 years, one with multiple sclerosis, and one who had a metastatic melanoma and has been in remission. Both have stayed on it, simply to make sure their disease doesn’t recur. They have had no side effects at all. I have been on it for 10 years—my wife, for close to that. I have had a number of AIDS patients on it for as much as 12 to 14 years with no side effects at all. There is no downside to it.