

“Maximum effectiveness of drug may not occur for several weeks or months after therapy begins. Maintenance therapy must be carefully adjusted based on patient tolerance and desired therapeutic response. Observe and monitor vital signs, especially while dose is being adjusted.”

On levodopa-carbidopa, *Physician’s Drug Handbook*, 9th edition, 2001, p. 589.

18. SUPPORTING OUR HYPOTHESES

THE BASIS FOR OUR THREE (OR FOUR?) IDEAS

Back in chapter three, when I introduced the key new hypotheses, I promised to give more details to support these ideas. Now that you have a PD vocabulary, an introduction to blood-brain barriers and addiction, and some brief case studies as examples, the time has arrived for the long-promised enrichment. You’ll even get an additional hypothesis thrown in gratis. This chapter will present a group of graphs from a recovering patient; it was the graphs from recovering patients that finally cracked open the mystery for us and enabled us to see what the drugs were doing, and over what time period.

Theoretical levodopa timetable – the old theory

If you recall from chapter three, levodopa and all the other anti-PD meds are supposed to be taken at dosage rates that ensure a steady On throughout the day. One to four doses, depending on the drug, over the course of the day will supposedly yield a steady level of dopamine. After the first dose of the day brings a person up into the effective, or On zone, regular dosing should maintain a person in the On zone, with maybe a few unavoidable moments of excess movement.

As you will recall, the chart for this theory showed a series of nice neat curves, corresponding to each dose, which rise smoothly, reach a gradual peak, and then taper off.

Chaos from overmedication – the new theory

However, the actual charts we saw tended toward the chaotic. In the first few years of our research, when most of our medicated patients were dyskinetic, On-Offing, and therefore obviously overmedicated, the charts of daily On-Offs did not support the idea of a uniform period of pill effectiveness as advertised. In fact, the reason I asked patients to start keeping track was because their verbal descriptions of their past week sometimes made no sense according to the descriptions of pill function according to text; I assumed that their reporting was suspect. When they charted their On-Offs, most of them had either unpredictability or, if there was any daily pattern at all, a pattern of daily Build Up. At the time, the Build Up did not look like a “pattern” – it just looked like late-in-the-day pill failure. It was only later, when we hypothesized that drugs could accumulate far beyond their conjectured half-life that the pattern of drug failure late in the day became obvious to us. Prior to that, daily Build Ups were inexplicable.

It was only when some patients started reducing their medication and waiting several months to assess the change that we started seeing charts that had regular,

predictable Ons and Offs as described in the section on daily Deficits. (Deficit days featured pill failure of the morning doses but increasing pill effectiveness later in the day.) Those charts were described in chapter 13, and they started us in the direction of looking for accumulation effects, including freezing (which looks for all the world like pill failure), after which the Build Ups began to make sense.

Finally, the wildest, most unpredictable patterns occurred when *recovering* patients with daily patterns did not, for whatever reason, reduce their medication quickly enough. We started seeing extremely chaotic graphs. These cases of unparalleled unpredictability and adverse effects were the final piece of the puzzle for us, confirming the weakness in the previous theories of drug application and suggesting the new hypotheses that we are presenting here. We were forced to conclude that, despite all the opposing information in the guidebooks, the wildly unpredictable charts of the mildly-dosed, recovering patients must be due to a previously unsuspected *long-acting* effect of the pills. Certainly, none of their charts conformed to the theoretical model.¹

Because these were the charts that clinched our burgeoning hypotheses and made, most dramatically, the point that dopamine-enhancing drugs taken days before have a huge impact on a following day's pill effectiveness, I will give here an explanation of Sonny's charts.

Sonny's situation

After being in our program 3+ years, Sonny broke his hip. The following charts are from a period five months after his hip replacement surgery. After the surgery, he increased his medication from 350 mg L-dopa/day to 400 mg/day. When Sonny had started with us he had been taking a high of 1200 mg L-dopa/day. He had slowly, over three years, gotten down to 325 mg L-dopa and 1 mg Permax per day from a high of 1200 mg of L-dopa plus 4 mg of Permax per day. During his decreases, he'd had cyclic periods of increased immobility, severe depression and/or anger, but more consistent, predictable Ons, and less dyskinesia. During his Feelin' Good days at the end of each reduction cycle, he would have some days when his new, lower dosage level worked perfectly: these halcyon days would have little or no Off time and no dyskinesia. However, this condition would change quickly as the drugs became once again – due to recovery – excessive. As the dyskinesia returned at the new, lower drug level, his wife would make another reduction. His reductions were always modest, and he never experienced full-blown drug withdrawal. He made new decreases each time the dyskinesia returned, based on his wife's assessments.

After several years of working with us, he had recovered the ability to smile. At night, more than 8 to 12 hours after taking his evening pill, he could increasingly move his arms and legs by himself – a level of pill-free movement that he had not been able to do for several years.

However, after breaking his hip, he lost all interest in reducing medication and, at his surgeon's suggestion, decided to keep his medication at a level admittedly higher than

¹ Of course, some patients were still getting very good coverage from their drugs. We weren't looking at their charts; only those of our pioneers who were experiencing Ons and Offs were graphing their results, writing up prose accounts of their day, or giving me oral histories of their drugs' daily effects. Patients who were fairly new to the drugs, who were still in the honeymoon period of drug effectiveness and whose drugs still worked uniformly all day, had no reason to chart their daily ups and downs.

necessary (admitted by both Sonny and his wife). For the first few months, he felt just great with the increased medication. Soon he began to complain about the increasing Offs and dyskinesia, but due to residual pain from the surgery and difficulty in using his repaired hip, he was reluctant to begin a decrease cycle again. During the preceding years of drug decreases, he had noticed predictable, cyclical, slowly-changing patterns of On-Off, Build Ups, and Deficits as his meds slowly cycled from excess to deficient and back to excess over a period of many weeks for each small reduction. Now, at 400 mg/day but recovering, his charts returned to being even more unpredictable than they had been when he was taking (unrecovered) 1200 mg/day – nearly three times as much.

These charts come from his post-surgery period, and will show what happens when a grossly high level of overmedication is maintained.¹ His medication levels were quite low according to modern prescribing practice – only 400 mg/day of L-dopa in a patient who had had Parkinson's for over twelve years. However, prior to the surgery, he had been moving well at 350 mg/day and was on the verge of making another decrease in his medication just before he broke his hip.

The most significant thing to see in his charts is that no two days are the same. This in itself contradicts the old half-life theory used in creating prescription advice. Instead, the Ons and Offs have almost no relationship to the time the pills are taken. At this new phase of his relationship with the medication, he usually takes the pills at the same time every day, only making once-in-a-while decreases for one or two days if he is feeling a severe worsening of adverse effects. Even so, some days the charts are almost opposites of the day before. A person whose medication is creating a consistent pattern can usually tell at what point in the day the medication becomes excessive (creating Offs, ticcings, or dyskinesia). However, when a person is completely over the top, every day's drug response can be a reaction against the *previous* day's or weeks' excesses, and it is anyone's guess how the brain will cope with the relentless onslaught of dopamine.

Sonny's wildly fluctuating charts are typical for a recovering patient who is having "instability" with his medication. We now suspect that any patient with Ons and Offs that are unpredictable from one day to the next, as demonstrated in these charts, is grossly overmedicated. The tidy, repeatable daily patterns, described in the preceding chapters, only occur if a person's medication is somewhat reasonably close to the amount that he needs.² When a person starts having patterns such as Sonny's, he is gravely overloaded.

Reading Sonny's charts – the new theory

In the following charts, this key applies:

- 1) The small black triangle denotes the time of day of the dose.

¹ Overmedication in this case refers to the amount needed by the individual, not an absolute amount.

² This statement only applies to those who are already having On-Offs. A person who is new to the drugs may not yet be having On-Offs. This absence of On-Offs is NOT proof that their drugs are being taken at the correct level. It can take several months, even years, before the brain of a PDer constructs enough defenses to enable itself to protect itself against excess medication via dyskinesia, On-Offs, and other adverse effects. Non-PDers using these drugs will manifest problems much sooner (see: Oliver Sacks' research). The reason for this difference is explained later in this chapter. Again, a person who is fairly new to the medications can be seriously, invisibly, overmedicated but not yet having On-Offs. By the time On-Offs appear, lasting brain damage has probably occurred.

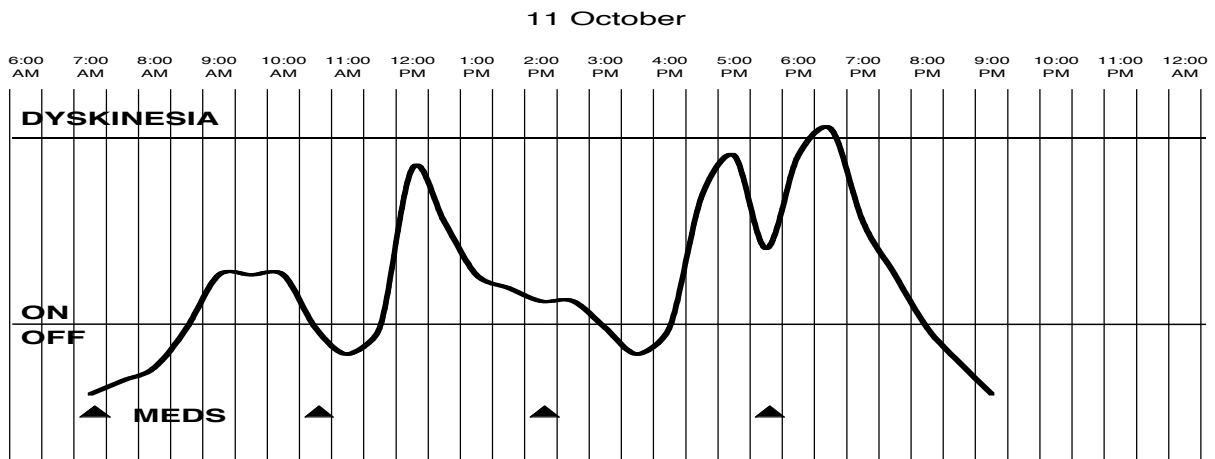
2) The doses were all the same size – a pill of 25/100 Sinemet and .25 mg of Permax.

3) The line denotes motor activity.

4) When the motor activity line drops below the Off line, Sonny could not move at all, nor speak. He was absolutely frozen. When the motor activity line was in the middle part of the On zone, he could move, but not optimally. When the line was in the low part of the On zone, he could shuffle, speak in a whisper, and move if he was given a push from time to time. His posture was hunched, he drooled, and had little small motor function. When the motor line was just below the dyskinesia line, he was moving optimally, smiling (though he had not been able to smile at any drug level prior to starting Tui Na therapy), and his voice was strong.

To collect the data for the charts, his wife asked him every hour how he was doing. If he could talk, he decided where the dots should go on the chart. If he could not talk, she decided. At the end of the day, they connected the hourly dots to create the following charts.

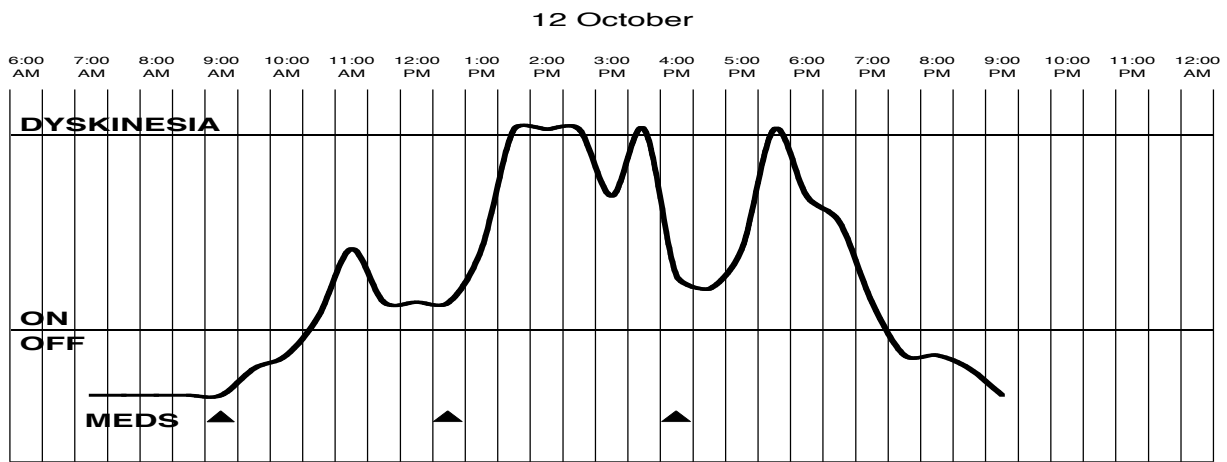
Prior to the hip surgery, Sonny's days began with his movement just barely above the On line, even before his first pill of the day. This meant that more than twelve hours after taking his last pill of the day the evening before, he was moving, albeit very slowly, on his own. After increasing his drugs (following hip surgery), he lost his ability to move in the early morning (pre-pill), and could only move after his first, or sometimes second, pill.



The first dose on October 11 created a nice On, followed by a predictable Off. The second made a spiked On, followed by a rapid decline in functionality.¹ During the decline from the second pill of the day, he took a third pill, after which he was immobile for 2.5 hours. Then, *just before* taking another pill, he shot up to a period of high mobility, with a small amount of dyskinesia. He started to plummet from this dose, but took a pill mid-plummet. Nearly twelve hours after his first pill, when motor receptors that had been shut down by his first dose were just starting to be receptive again, he took his last dose. The resumption of effectiveness in the motor area, combined with the

¹ Review: as noted on the preceding page, Sonny used the low region of the On to indicate that he was able to move, but only very slowly. The Off section was used when he was utterly immobile, unable to initiate any movement, including speech.

accumulation of dopamine throughout the day, caused the fourth pill to appear to be immediately effective: this dose propelled him into half an hour of arm spasming, facial grimacing, and shoulder twitching. Two and a half hours later, he was already Off and crashing. He would be completely immobile until two in the morning, at which time, *without having taken medications since 5:30 the previous evening*, he would again be able to move slowly but steadily, using his arms to adjust his blankets, moving his legs to change position, and to speak softly for several hours. However, this spurt of night-time (drug free) movement never lasted until the first pill of the morning, as it had in the previous year. Instead, it would usually sputter to a halt at around 5 in the morning.¹ He would be completely Off again when it came time to take his first pill of the day and begin the On-Off routine once again.

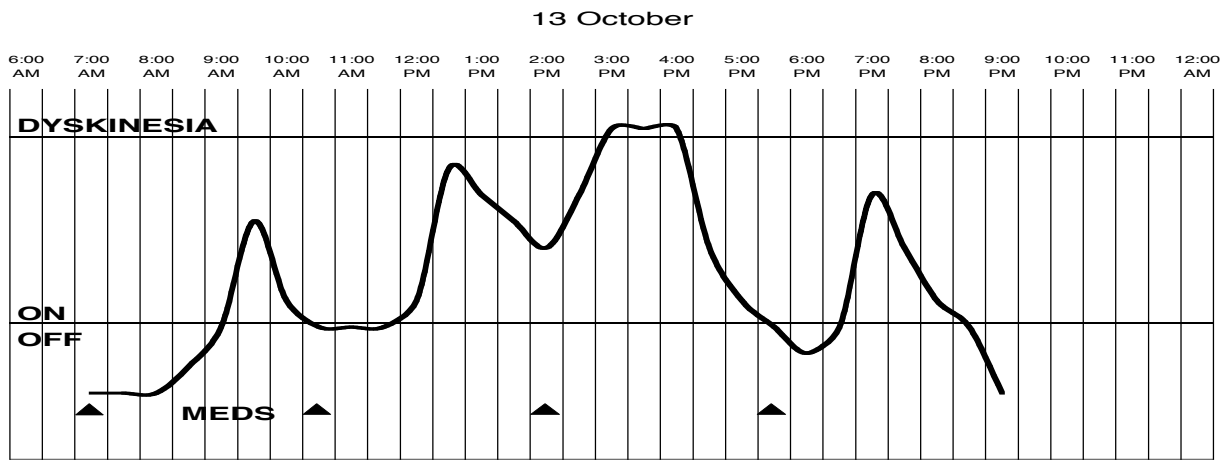


On this chart, Oct. 12, the ups and downs are almost the exact opposite of the day before (Oct. 11). Because of the dyskinesia the day before, on this day he only took three pills, spaced further apart. It took nearly two hours for his first pill to work. He moved well for 20 minutes and then went back to shuffling. Sonny usually took his second pill of the day by 10:30, but his second pill on October 12 was delayed to after noon. However, even with the delay, his second pill led to dyskinesia for most of the dose, except for a brief Roller Coaster down into normalcy and then back up to dyskinesia, again followed by a rapid decline. He was moving well two hours after taking his third dose; however, it soon spiked up into dyskinesia and then slowly climbed down. He was

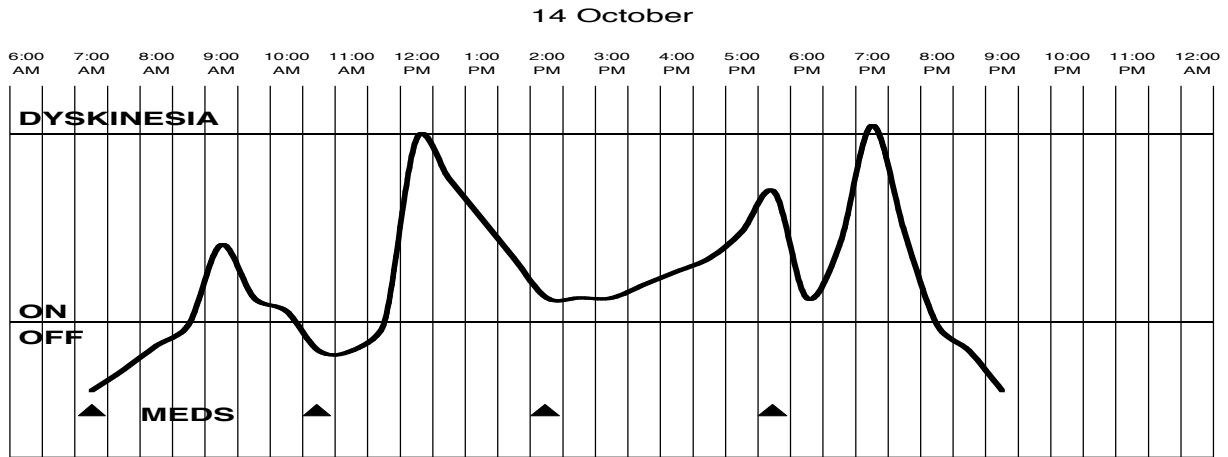
¹ This specific phenomenon will not be discussed in detail in this section, but let me note that this unfortunate decrease in mobility during his 14 hour “unmedicated” span, from 5:30 in the evening until 7:30 the next morning, was most likely due to drug-induced brain damage from overmedication. Prior to this time, during his recovery, before he increased his medication back up, he started having “unmedicated,” night-time movement, movement that was very different from his On time. It appeared to be coming from native dopamine. This night-time movement would emerge 8.5 hours after his taking of his last dose, ending his profound, crashing bedtime Off. When it first appeared, he could only move one arm for less than an hour. After four months, he could move an arm and a leg, and the movement lasted for two hours. It took over a year for the night-time movement to include all four limbs and sustain – get this – until he took his first pill of the morning. After taking his morning pill, he would plummet into a severe Off (see: switching), go On half an hour later, and then, two hours after that, crash into a frozen Off. Interestingly, the last limb to finally acquire what we named “Sonny’s night-time movement,” a slow, rather languorous, weak/gentle movement – very different from his medicated On movement – was his left arm: the very limb in which the Parkinson’s symptoms had first appeared.

off for the day within three hours after his last dose. He typically crashed “very hard” by the end of the day.

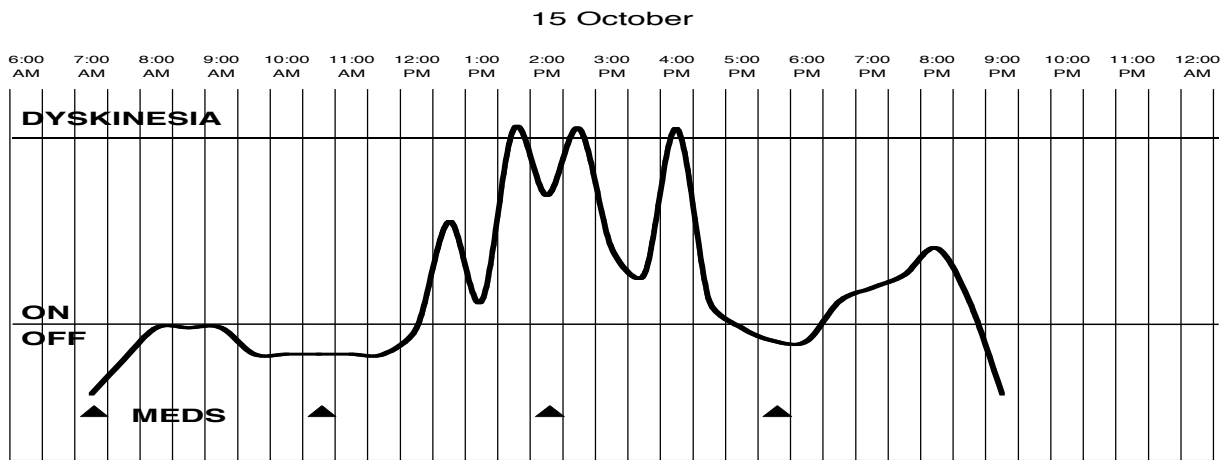
Remember, during a roller coaster type of response to the drugs, the movement line on the chart will go down while the amount of drug in the body, based on time of dose, is still going up.



Unhappy with the slow movement of the day before (Oct. 12), when he had only one hour of good On time up until 1:30 in the afternoon, he went back to four pills (400 mg levodopa) on Oct. 13. Aside from the slow start in the morning, this was a very good day. Due to the decreased dose the day before, he had very little dyskinesia and only a few hours of Off in the morning and a few hours of Off in the late afternoon. This is the sort of several-days pattern that had first led us to suspect that the effects of any given pill were being influenced by pills taken the previous day.



On this day, Oct. 14, he paid the price for having gone back up to four pills a day the day before: his first On of the day was earlier, but the subsequent swings were more abrupt. From 10 to 11, he was moving very slowly and, except for a brief surge at 12:30, continued that way for almost the entire afternoon. (Remember, movement in the lower On zone was shuffling, drooling, and whispering. Normal stride and function was indicated in that part of the On zone just below the dyskinesia line.) His 2:00 p.m. pill didn't work until after 5 p.m., and then it Roller Coastered up, dropped abruptly, and was starting back up when it combined with his evening pill to create dyskinesia.



This day, Oct. 15, is almost the exact opposite of the day before, though he took his pills at the exact same times! On this day, he is clearly overmedicated: even his first pill of the day won't work – his brain is still oversaturated from the day before. His brain builds such a level of resistance when he adds his second pill to the mix that he is able to get On, into the functional zone, only at the tail end of the second dose, as the dopamine levels are slowly forced down by the brain's frantic defenses, down from the immobilized, overmedicated zone.

It appears, from looking at the chart, as if the drugs have finally become sufficient at 1:30 p.m. In fact, they have finally dropped *low* enough that his brain is allowing some

movement. Since he is still somewhat overmedicated, this movement appears as dyskinesia. This is why, on the chart, he shoots up into dyskinesia even before he takes the third pill of the day. When the third pill starts to take effect, about an hour after the dose, he plummets back down into immobility as his brain becomes oversaturated with dopamine.

However, by now, some responses (neuron refresh – see chapter three) to the first pill of the day have been washed out of his system. Also, the Shut down, with its seemingly therapeutic respite and accelerated drug clearance functions, may have been at work. From these influences, his brain's dopamine level has decreased enough that he is able to get back some motor function (On) from the third pill. When this pill begins to wear off, he crashes, of course, after so much excess. After the crash, the last pill of the day works nicely, supporting our ideas that the shut downs seem to serve a therapeutic function and that the refresh rate for overstimulated dopamine receptors seems to be about twelve hours.

Please pause for a moment to look at the two charts on the preceding page. Remember – the pills were being taken at the same time every day, the doses were the same every day. Sonny's minimal physical activities and non-existent social life, due to his injured leg, were the same every day. Nearly all variables were holding in a consistent pattern, but Sonny's On-Off times appeared to be responding to something other than his dosages. **Only if** we theorized a cumulative property for the medication (which meant a greatly longer half-life for his pills than the doctors were using), and different rates of dopamine response in the limbic and motor areas, we could construct a model in which Sonny's drug results were not only explainable, but predictable.

Repeatable randomness

It did seem at first as if my interpretations of these charts were merely specious – random explanations for random events. I feared that I was just making things up to fit the case. However, using our new theories, we found we could predict exactly what would happen with Sonny, or with any other medicated patient, over the next few hours or the next few weeks. For example, every time Sonny tried a lower dose, he had the predictably slow onset with the overall good day. Every time he increased back up, the next day predictably would have more dyskinesia and the day after that would have a long delay before the morning On occurred, followed by predictable spikes of dyskinesia, a crash, and a nice dose at the end of the day.

Although the charts seem erratic and formless on any given day, they actually followed this pattern very nicely over time. Not only that, but all the other patients had similar patterns if they were grossly overmedicated. It was by noticing the similarities in their charts on the first, second, third, fourth, tenth, and fortieth day after a drug change or after becoming overmedicated that we were finally able to make a logical explanation for what was occurring. While there may be reasons other than the ones we are proposing (a certainty!) that more accurately pinpoint the reasons for the On-Offs of our patients, the fact that by using our new hypotheses we were able to predict fairly accurately which “unpredictable” pattern was most likely on any given day, week, or month, and how these patterns would most likely change over the long-term did suggest that our ideas were of value.

Naïve researchers

When we first started this Parkinson's research project, long before we knew the drugs were addictive or cumulative, we were naïvely expecting patient charts to be useful for our questions about two very basic aspects of the pills: onset and duration times. Our earliest questions were very simple: how long did it take for the pills to start working? How long did the effects of the pills linger?

Before we understood that there were changing thresholds and variable baselines, we assumed, as did the patients and their doctors, that we should be able to get somewhat consistent numbers for these easy-to-measure, straightforward events. We assumed, wrongly, that patients who were having Offs and Ons would be convenient subjects for measuring these events; patients who weren't having Offs and Ons usually couldn't tell very accurately when their drugs started to work, but in On-Offers it was obvious.

The common assumption at that time was that it was advancing Parkinson's that was responsible for Ons and Offs: this thinking held that, as Parkinson's disease advanced, the native dopamine further decreased, and this decrease in dopamine was the sole reason that, over time, the pills needed more time or a higher dose to start working. (This view completely ignores the manufacturers' warnings that the medications themselves cause Offs, freezing, bradykinesia and tremor, to name just a few of the adverse effects of pill effectiveness that can *resemble* their opposite: pill "failure.")

We measured the onset and duration times of the drugs in our patients who were having On-Offs. We defined onset time as the time it took from the moment the pill was taken until the time that there was a perceptible improvement in motor function. We defined duration as the time elapsed from the moment that pill-generated motor improvement appeared until the time that it ceased or significantly decreased.

We thought that there should be some consistent relationship between taking the pills, the time until onset, and the time when the pills wore off again. Instead, these are some of the numbers that we frequently observed:

Onset

- Almost instant
- 10 minutes
- 20 minutes
- Half an hour
- Forty-five minutes
- An hour
- An hour and a half
- Two hours
- Three hours
- Four hours
- Unexpected Ons more than six hours after dosing
- Never

Duration

- None
- Less than a minute

One minute
Five minutes
Ten minutes
Half an hour
Forty-five minutes
An hour
Two hours
Three hours
Up to eight hours

We had been expecting a nice, six-hour interval pattern. Ha ha ha.

Instability and unpredictability: some examples

One patient had predictable, one-hour onset waits, followed by predictable three-hour On times. Another had predictable half-hour waits followed by predictable three-hour Ons every morning, two-hour Ons every noon, one-hour Ons at 4:30, and no Ons from the evening dose.

Some pioneers were On most of the day, with random periods of freezing that could possibly be related to stress or bad weather. Some patients had utterly unpredictable results; some days they would feel great all day and the next day they could hardly move. Only patients who were pretty new to the drugs had a smooth pattern. Patients who had developed On and Off patterns had decreasing stability/predictability in their daily On-Offs.

This lack of uniformity, when a patient responds differently to each one of his doses, and/or the lack of conformity from one patient to the next is referred to as drug instability and/or unpredictability. Call it what you will, instability or unpredictability, none of the On-Off patients using levodopa had any pattern that seemed to correspond neatly to a three-hour half-life.

As we realized that there was no value in looking for predictable Onset and Duration times, we tried to ascertain just when and why the drugs, in any given person, switched from predictable to unpredictable.

Factors influencing unpredictability of the drugs

The onset of Unpredictability

There appeared to be two key factors influencing the emergence of unpredictability/instability: the number of years a patient had been taking the medication and the dosage level.

We tried to figure exactly how many years it was, after starting the drugs, that the drugs became unstable. However, the responses were so varied that they were statistically meaningless. For patients who had been taking the drugs to the point of On-Offs, or even to the point of feeling the surge and ebb of the drugs, no two patients out of our first group of fifty-nine medicated patients were the same. This lack of similarity made compilation of statistics unreasonable.

But in general, if a patient was fairly new (one to three years) to the medication and dosed cautiously, the Onset time and Duration were predictable for a few years –

namely, Ons and Offs never occurred, and it appeared as if there was a seamless transition from the effects of one pill to the next.

While the number of years before On-Offs occurred appeared to be a key variable, it did seem as if this variable was affected by dosage amount: patients who had been started at 300 mg levodopa/day and told to stay there as long as possible developed the On-Offs much later than patients who had been told after diagnosis to “start at two pills a day and increase by one pill a day until you feel really good, and then stay at that level.” Patients in the latter group had much higher starting doses, often getting as high as 800 mg/day levodopa before they “felt really good” and then maintaining that high amount as their “starter dose.” This group might have drug-induced dyskinesias and On-Offs within three to six months of starting the medication.

As recently as 1998, the available literature used to suggest that there was a five-year period before the drugs became unpredictable. The more recent literature suggests that a two to three year period is now the norm.¹ I suspect that this changing time frame has to do with the newer, bolder prescribing patterns. These in turn may have to do with our society’s increasing demand for quick results from medical intervention, or they may be related to doctor misinformation.

Certainly, in the first few years of dopamine-enhancing drug prescribing, when the drugs were still considered somewhat experimental, most doctors were keenly aware of the risks and adhered closely to the recommended dosages. Possibly, since these drugs have now become accepted tools, breezy nonchalance has replaced cautious trepidation.

For whatever reason, in our experience, the drugs are now being prescribed at much higher rates. My more recently diagnosed patients who were working with younger doctors invariably were prescribed higher starting doses and faster increase rates than my patients who had been diagnosed ten, fifteen, or twenty years earlier and who were working with older doctors.

For example, Old Dr. Rafferty’s long-time patients Hjalmar, who had been taking levodopa for over sixteen years, Mark and Honoria, both taking it for nearly ten, had started at 300 mg/day. Honoria was still at that level after ten years (plus two agonists). Mark was still taking 300 mg/day plus an anticholinergic. Hjalmar had increased slowly through the years, but his average increase was a mere 50 mg/day increase each year. They all still had a high amount of predictability in their drugs: as their Parkinson’s symptoms had gradually advanced over the years, Dr. Rafferty had added other drugs to their mix or suggested they use a walker. He usually gave them permission to increase slightly, but with a warning that the lower levels were safer, hence the slow increase rate for Hjalmar and the addition of a few other drugs for Honoria.

Dr. Rafferty’s long-term patients, in general, had far fewer problems with their medications, even after twenty years on the drugs, than the patients of the other, younger, local neurologists. I did notice that even Dr. Rafferty was starting to be bolder with the drugs, however; his more recently diagnosed patients had been started at much higher levels. He even complained to one patient who was reluctant to go above 500 mg/day that, “All my other patients are taking at least 800 mg/day and there is no problem.”²

¹ A.N. Lieberman, MD, Curing Parkinson's disease in our Lifetime: Part 3, Parkinson Report, Fall 2000, Vol. XI, 3, National Parkinson Foundation, Miami, FL, pp. 10-12.

² Considering that I was working with several of his long-term patients, two of whom were taking 300 mg/day, and one having dyskinesia at that low rate, I must question Dr. Rafferty’s accuracy.

In summary, it appears that the size of the dosage and the number of years one takes the drugs affect the onset of unpredictability.

Mood

We also noticed a factor that related to short-term drug unpredictability, those unexpected On-Offs that might happen on any given day. Mood, it appears, plays a large role. A visit from a dear, out of town friend might coincide with the drugs working all day, with no Offs. An unexpected diagnosis of early stage, easily treatable melanoma or prostate cancer, on the other hand, was accompanied by little or no On time in the weeks or months that followed.¹

None of our patients' charts looked like the orderly theoretical one at the start of chapter three, page 37. Most ranged from mildly predictable to completely random. What was the reason for this "instability" of dopamine-enhancing drugs?

Forming the hypotheses

More about half-lives

As related earlier in chapter three, we were assuming, as were the doctors and researchers, that the significant number to keep in mind with regard to dosings of DEDs was the half-life. The half-life of a drug is the amount of time it takes for 50% of any given dosage to be broken down and/or excreted from the body.²

¹ These examples are drawn from our patients: Hjalmar was diagnosed with prostate cancer. He did hormone treatments, and happily, his PSA levels are now below normal. His drugs did not work well until he got the blood test showing his PSA levels were down. The sores on Mark's face were skin cancer. They were removed and he received a good prognosis. His drugs, however, completely failed him for over two weeks, from the time of diagnosis until the scabs from the cancer removals (the cancer spots were frozen off) started to crumble.

² The half-life of a drug is *not* like the half-life of radioactive materials. Radioactive materials have a steady rate of half-life. Here is an example of radioactive half-life: The radioactivity of a hypothetical ore is depleted by 50% over, let's say, 100 years. We would say that the radioactivity in this ore has a 100-year half-life. We can be certain, based on the nature of radioactive decay, that during the second 100 years, 50% of the *remaining* radioactivity will be depleted. In yet another 100 years, 50% of *that* remainder will be gone, and so on. The first span of 100 years is referred to as the first half-life, the next is the second half-life, and so on. In this hypothetical radioactive ore, the half-life rate of 100 years remains constant; in this example, it will always take 100 years for the remaining radioactivity in the ore to degrade yet another 50%.

Half-life in the body is not so steady and predictable. Many factors can alter the rate at which a drug is broken down or excreted. For example, much drug breakdown occurs during the drug's first pass through the liver, when food absorbed from the digestive tract goes to the liver for a first cleaning before entering the main bloodstream. Also, drugs making it through the liver might be stored indefinitely in fatty tissue for later use. Drugs might even be broken down quickly one day and not so quickly the next, because of emotional, hormonal, or even weather-related influences. So many external and internal events can affect the rate of drug processing that it is impossible to accurately predict how long it might take for the second 50% to be broken down halfway. As for the remaining bits in the third or fourth half-life, it is anyone's guess.

Official half-lives of drugs (the first half-life only; the others are ignored) are usually determined using a small test group of college-age students. Researchers are fully aware that drug half-life in an octogenarian can be many times longer than the "official" half-life of that drug. In some cases, a drug that is half removed from a college kid in a few hours might linger in an older person for days. However, since oldsters are so variable, they are rarely used for research. (Footnote continued on next page.)

As noted in chapter three, it had been established decades earlier, based on blood work, that most anti-PD drugs have a fairly short life span in the blood. In the case of L-dopa, for example, half of the medication was gone from the blood within a few hours of ingestion. Mirapex had a half-life of 8 to 12 hours, Permax was 24 hours, and Eldepryl was 48 hours, to name a few. The dosage schedules were built around these numbers. I had sat in on a lecture in 1998 in which a drug representative had assured the audience of PDers and caregivers that the best interval for taking levodopa-containing pills was every six hours, and that this was based on a half-life of approximately 2 to 3 hours.

Build Up questions

It wasn't until two years into our study, after looking at these charts that never reflected anything resembling a two-hour half-life, that it hit me like a ton of pills that the levels in the blood were a side issue. The significant number should have been the level in the brain.

We also realized that no one knew if PDers, whose dopamine levels were low, might also have altered levels of dopamine-related chemistry. For example, were the breakdown mechanisms for brain dopamine *elevated* in PDers? *Diminished*? Did anyone have any idea whatsoever how long or in which part of the brain these drugs lingered after they got inside the blood-brain barrier? No.

What was the reason that, according to the manufacturers, these drugs might take several months to attain a therapeutic effect? Was a slow amassing of dopamine in the brain the cause of the delayed therapeutic effect? In that case, if the drugs *could* accumulate over months, and some people were being prescribed doses so large that the drugs worked within a day or two, they might be amassing nearly thirty five times more drug in their brain than they actually needed. If so, no wonder these drugs rapidly became unpredictable!

Application of this idea to all dopamine-enhancing drugs

The slow accumulation of dopamine, if it was occurring, would not be just an L-dopa problem, but a problem with *any* dopamine-enhancing drug. As an example, Eldepryl has a much longer half-life than L-dopa: two days. Therefore, the suggested dosings of Eldepryl are further apart than the dosings for levodopa. And yet, was this half-life number actually significant?

Some metabolites (breakdown by-products) of Eldepryl pass out through the kidneys. Others get into the brain and are passed out...when? Who knows how much is still in the brain when 50% is still in the blood two days later! The process by which these metabolites are broken down in the brain isn't known. They could be lingering in there for a week, a month, a *year*, and no one would be the wiser.

The theories of medicine, in an attempt to conform to an "objective" model like the still current Cartesian (René Descartes) theory of body = soulless mechanism, discard the evidence that no two people are alike and, instead, use only those healthy humans that have the greatest degree of similarity for their research. They imagine that this makes their work more scientific. Maybe it would be so, if their results were only imposed on those youthful, relatively similar students.

But if *medical* research is done on uniformities and the results imposed on variants, practitioners of such medicine lose their claim of objectivity and "scientific logic." This subject is beyond the scope of this book. But it is worth noting that, although half-lives in biology are NOT similar to half-lives in radioactive ore, the numbers are traditionally applied as if they were.

Because all the dopamine-enhancing drugs work in the brain, and we have no idea how long they last in the brain, we are in the dark about the true effective times of all the dopamine-enhancing drugs, not merely levodopa.¹

Stabilization theory

The suggested doses of these drugs are usually determined by how a person is feeling on any given day, combined with the half-life information. An outgrowth of this method of calculating drug effects is the current, dangerous theory of psychotropic drug stabilization.

Based on the methods of the three doctors who tried to stabilize Zoe, Birdie, and Viktor when they became dangerously addicted, and on six similar cases reported to us from PDers and health practitioners across the USA, England, and Spain, I can say that 100% of the doctors in this admittedly limited sampling assumed that even extreme cases of drug problems could be “stabilized” within three days.² In every case, the results were ghastly or deadly.

We had to conclude that there was something seriously wrong with the current method of assessing drug levels, determining doses, or stabilizing patients with medication problems. But wait! Hadn’t government-approved testing shown that these drugs were safe?

Drugs pass tests

Yes, all the drugs had passed through various scientific tests prior to being unleashed on the public.³ But what these tests showed was that the drugs appeared to

¹ Again, the reason we have used levodopa so often in these examples is that it is the most commonly prescribed drug for PDers. However, the principles apply to any drug that increases brain levels of dopamine.

² Both Zoe’s and Birdie’s doctors were Parkinson’s specialists, engaged in doing PD drug research. They both currently rely on the blood half-life assumptions.

³ For an example of the sort of mentality that exists in “scientific drug testing,” the *Awakenings* researchers (very brilliant, competent doctors, actually, and Oliver Sacks is a genius), in 1968, assigned drug doses based on the half-life of L-dopa being 1-3 hours. Patients were given different doses once every day in an attempt to figure out what the ideal dosage would be. Knowing that the half-life was a mere 1 to 3 hours, the logical assumption was that the L-dopa was effectively out of the bloodstream within 24 hours. This meant that every day, the researchers could presume that they were starting with a blank slate. If a patient did not respond on day one to 1000 mg of the drug, the next day they might try 2000 mg. Or conversely, if they noticed on day four, at the 4000 mg level, that the patient was showing signs of overmedication, the next day they would try 3000 mg. This makes sense, based on the half-life theory. It also makes sense according to the theory that all brain nerves work at the same speed. A motor response was the “dipstick” test: if a previously immobile person could move, the researchers assumed the whole brain was topped up exactly right.

Those researchers found that, even in patients who responded well at first, after many days had gone by, the same dose behaved unpredictably; sometimes a patient would have worse side effects on a day with a lowered dose, and sometimes a patient wouldn’t seem to respond at all to increasing doses, and then, wham! He might erupt with life and vigor on a day with *decreased* medication. They concluded, eventually, that the drug was not stable or predictable, and, as the treacherous side effects appeared, that it was also unsafe for any person.

But the point here is, just because a drug has been tested doesn’t mean much. We all know of drugs that make the headlines because they turn out to be toxic, even though they had passed through “rigorous” tests years earlier. The problem, to a large extent, may be that the companies that do the testing

have some benefit, and that people didn't immediately die from them. The tests also established that some of these drugs might not reach full effectiveness for six to eight weeks, a point ignored by all the doctors in our (clinic, travel/lecture, and email) experience. Nearly every doctor that we have heard about has been confident that the PD drugs should reach effectiveness within three days. In the case of Mirapex and Requip, two drugs that are started at low levels and gradually worked up to a higher level (due to these drugs causing fainting and other unpleasant side effects against which the patient must slowly become hardened), the assumption remains that, once the "effective dosage" is attained, the full effect will be obvious within two or three days.¹

have a vested interest in the results. That subject is beyond the scope of this book. But it may be more than financial interest that influences our interpretations. Maybe it is human nature to perceive results through paradigm-colored glasses.

Actually, there is a new field of science devoted to trying to figure out how to make tests be meaningful. But so far, no one really knows how to best interpret the results of all scientific testing, medical or otherwise. Medical testing is, however, recognized as the least scientific kind of testing and the most worthless for predicting results. The entire idea of scientific testing may be a fallacy. The newest theories of physics indicate that, due to the profoundly interrelated nature of all aspects of the universe, in order to correctly determine which event is causing which result, one must either intuit the answer or, in order to make an accurate logical construct, actually know all the initiating events since the beginning of time. Short of using one of these two systems, no "scientific" field of enquiry can actually enable one to make meaningful predictions.

The most basic example of this problem is the old statistics class model: no matter how many times a dropped coin might come up "heads," the odds will remain 50/50 for a result of "heads" with each new drop. The coin may appear to have only one side – the head side – to the foolish observer who imagines that a series of "heads" means that no "tails" exist! The sad truth is this: a given result implies no predictability of the future. Nor does a seeming relationship between two events prove which is cause and which is effect, if any. For example, hundreds of years ago experiments "proved" that a slab of beef wrapped in a dirty shirt and set out in the sun would create living maggots. This appearance of life being generated via two lifeless commodities was "scientific proof" of the theory of Spontaneous Generation, and was frequently used in support of the biblical story of Genesis. Incorrect guesses by centuries of "leading scientists" (see: any good book on St. Thomas Aquinas) should have confirmed the impossibility of "scientific" prediction or proofs by now, but ignorance and ego die hard.

The concept that only intuition and/or knowledge of the origin of the universe can provide truly correct, truly accurate predictions has only recently been demonstrated by western scientific methods in the field of physics, but it is an old, respected Taoist, Vedic, Buddhist, Jewish, Islamic, and Christian principle. In the west, a widely known statement of this, now "scientifically" confirmed (see: any good book on Chaos theory), truth is found in the Hebrew Psalms: "Seek ye first the kingdom of God...and all other things will be added unto you." Wisdom, which includes the knowledge of all forces in the universe, where they are going and what action is precipitating which result, is among those "other things" promised in the psalm. Wisdom, even scientific wisdom, comes to him who seeks not *facts*, facts always incomplete, always perceived through the veil of the current paradigm, but the font itself – the Origin of Wisdom.

Where I am going in this overlong footnote is this: testing does not equal safety, a medical degree does not confer wisdom, and the material taught in medical classes changes as rapidly as the weather. We do scientific experiments to determine whether or not events have some degree of repeatability, and then guess at the meaning. The ultimate conclusions for the experiments, the "why" and the "how will it play out for any given individual," remain mysteries, known only to those who transcend their superstitions, "scientific" or otherwise, and delve into the heart of God.

¹ We have seen that patients who stay at the "sub-therapeutic," starter levels of Mirapex actually do obtain good benefits from the drug, but at these low levels it can require several months before the benefits become obvious.

Two dopamine systems?

But resuming our proposal that these drugs accumulate slowly, this hypothesis created still more questions. For example, if dopamine accumulated slowly, why did so many drug-users, after just a short while on the drugs, have obvious signs of motor function improvement within an hour or so after taking a pill? Was it possible that the motor function, separate from the limbic area, could make a visible flash of response to a flush of incoming drugs and then drop away as blood levels dropped? We were pretty certain that something was going on that took ten weeks to develop, and yet the motor response to drugs was sometimes so quick. Why?

The simplest way to explain this would be the existence of two systems. If we proposed that motor function had a quick response to dopamine as it crossed over the blood-brain barrier, but limbic response was slow, the seeming conflict would evaporate.

More questions

If that was the case, was motor function related to blood levels, but limbic function was not? And if so, how could we tie in the observation that the brain employed the motor area in dyskinesia when attempting to discharge excess levels of limbic build-up?

Did the limbic system act as a reservoir? Could the limbic area continue to slowly stash dopamine into receptors and vesicles even while the motor area appeared to be losing steam as the blood levels receded? Might the motor zone's quick processing of a blood-borne surge of dopamine allow for a visible, short-term burst of movement, while the limbic area was slowly filling up? Did the incoming dosage ride *on top* of the existing limbic amount? Was it easier to get a motor response if the limbic area was already filled, or was the motor area acting completely independently of the limbic?

And what about the very distinct effect of mood on whether or not a drug performed as expected? The frontal lobe is considered the place where mood is regulated. What was the time frame for dopamine retention/processing in the frontal lobe?

Three systems?

What if the limbic level was supposed to serve as the baseline, a baseline that, in a healthy person, would always ride just a hair's breadth below the motor threshold? Next, the mood and thinking area might be the activator, the place that determined whether or not movement should occur. If the brain was perfectly in tune, possibly the dopamine levels were at equilibrium throughout the brain, poised, with almost exactly enough dopamine floating about, but not quite enough to trigger a movement. Then, when a thought of movement occurred, the frontal lobe might initiate a neurotransmitter release that led to the release of exactly enough dopamine to the motor area. This dopamine would stimulate a nerve, thus opening the way for the acetylcholine brigade, which in turn would perform the actual mission of pulling on the muscles.

We in the project now feel strongly that dopamine is not a movement inducer in the same way that acetylcholine is. Dopamine is primarily a health, mood, and will power related neurotransmitter.¹ When a person is relatively pain free, warm, and not under

¹ Not will power in the sense of fear- or panic-driven ability to perform: these forms of drive come from adrenaline. This dopamine-related will power would be the will that is attuned with joyful dynamism: contemplative, intuition- and wisdom-driven will.

stress (limbic zone issues), and the mood/mental condition is healthy (frontal lobe), these two areas are then able to trigger a release of dopamine into the motor initiation zone as needed.

This is actually a new idea (yet another hypothesis!):

**Dopamine does not provide movement; it provides the transition between thought and movement.*

This would explain why, when people begin to recover from Parkinson's, they are often astounded at how they need only to think of doing something, and they find that they have done it.¹

Dopamine: a multi-purpose neurotransmitter

In order to create a logical system that could account for all the various time frames and the influence of mood, we had to propose this tiered system of dopamine distribution with its variable time frames for processing dopamine, and this idea of equating dopamine with thought-to-movement initiation, rather than movement per se. If this was correct, it meant, conversely, that the old ideas were incorrect.

In the past, researchers might have noted the satisfactory, though brief (three to six hours) motor response to the drugs and assumed that was the whole story. But of course, until just twenty years ago, dopamine was deemed nothing more than a muscle relaxant (see: appendix 5). Now, in the present, researchers are just starting to see that dopamine may have more than one or two parts to play. We applaud these researchers and suggest that there are even more ways in which dopamine plays a part. In fact, we are proposing, by the end of this chapter, that dopamine is a key regulator for multiple systems, so long as a person is not in a condition of emergency.

The usefulness of hypotheses

In science, when we arrive at possible answers to our questions, these “educated guesses” are called hypotheses. They are different from established facts. The hypotheses that we have made about dopamine processing in the motor area, frontal lobe, and limbic system were made in response to our musings about the seeming conflicts in the long- and short-term responses to dopamine.

One of the important tests of a hypothesis is whether or not it has helpful applications. The hypotheses that we made about brain areas were very helpful in helping patients reduce their medication. By assuming that the motor response was only one small part of the story, our pioneers were able to gird themselves for the rigors of drug reduction. By our proposing that the invisible limbic area was making productive changes

¹ One patient, Lynne, a completely recovered patient (who never took the medications), started crying the first time that she realized she had stood up from the sofa the moment that she thought of the action, without having to first summon up any sort of momentum or thinking about why she needed to stand up. What made her cry was that she had never known how easily the “rest of the world” stood up from a sofa. She had just assumed, all her life, that her way of deciding to move and then moving was normal. But when she got up without even having decided to do so, simply by having the thought “maybe I should stand up,” she cried in uncharacteristic self-pity, “Is this how easy it has always been for everyone else?”

even when the motor function appeared to be missing in action, the pioneers were able to plot a long, ten-week course of drug reduction through what would have otherwise seemed a pointless exercise in self-denial.

Many pioneers had tried to reduce their drugs in the past to deal with their worsening dyskinesias. Few had ever gotten past the end of the ten-day Slide. When their bodies became much worse than they expected, the pioneers had regretfully assumed that they simply could not reduce their medication: their Parkinson's had advanced too far.

By using these new hypotheses, we were able to see, time and again, that drug reduction was a possibility. Not only was it a possibility, but the cyclical nature of the patterns that emerged during drug reduction gave further support to the hypotheses.

At some point, because of conflicts with doctors and friends of patients, we needed more than just helpful hypotheses; we also had to confront the increasingly obvious fact that all of the officially proposed drug dosing theories were wrong: the blood half-life of a psychoactive drug had very little to do with the true effective period of the drug. It kept coming back to this blindingly obvious but ignored concept: the combined different drug levels in each part of the brain should determine the effective period of a psychotropic drug. Unfortunately, while our research anecdotally supports this premise, we have no hard and fast tallies of actual dopamine molecules in the brain to support our findings.

But, in the end, we have decided to use our new hypotheses as if they have been proven. We needed conclusions that could be used by our patients, regardless of what the actual physiological processes turned out to be. Therefore, while this idea is based on no published research from the old paradigm, nor measured by any machine, it is supported by the tens of thousands of hours of actual drug results reported by our pioneers, and we sponsor it as a working hypothesis.

How can we get concrete proof?

Determining an individual's drug levels mechanically, using an as yet not invented scanner, would still require a tremendous amount of math. All the parts of the brain are probably sharing dopamine back and forth in an ever-changing flow that might vary with the speed of thought. So many events would need to be considered. Just for one example of the floating nature of dopamine, let's consider sleep time, when the movement initiation centers are shut down; the dopamine hasn't disappeared. Does some of this unused dopamine drift down into the limbic area, where it gives us the peaceful feeling and ease that we should experience in sleep? Where does the dopamine go when it moves back and forth between one spot and another? Yes, it gets stored in vesicles, but how much, and in which ones? So many things to ponder! The one-plug-for-one-hole theory of brain science is passé. How can we possibly measure the quantities of these shifting sands?

Due to the complexity of brain factors, together with the absence of appropriate tools, it is understandable that brain lives or half-lives for these drugs have never been measured. Not one drug company is working on determining brain half-lives for these drugs. Because of the blood-brain barrier, which makes dopamine levels inside the brain

different from the levels in the blood, it is simply too difficult at this time to determine the actual amounts of dopamine in the brain or the dopamine half-life.¹

However, measured or not, this hypothesis was helpful to our patients, and it made sense of otherwise inexplicable unpredictability and instability. As for the accompanying hypotheses suggested in this section regarding specific rates of dopamine retention and prioritization in the limbic, frontal, and motor areas of the brain, these have already been hashed over in chapter seven and will not be discussed further here.

And so, further supported by Sonny's charts and the charts of many others like him, we feel we can, with some degree of confidence, present again our hypotheses, further bolstered.

HYPOTHESIS 1 - THE EFFECTIVE DURATION OF DOPAMINE-ENHANCING DRUGS

Our hypothesis that the significant research number when measuring drug effectiveness of psychotropic drugs should be the amount of time the drug is effective in the *brain*, and not the blood level half-life measurement, is pure common sense. We propose that, in order to determine this number, all aspects of dopamine effectiveness, including a possible accumulation effect, must be considered. Although there is no way to measure these events at the current time, they may be extrapolated from patient data. It appears that there may be a multiplicity of factors involved in determining the lifetime of effectiveness of dopamine-enhancing drugs. The following is then, our first hypothesis.

The effective duration of all dopamine-enhancing drugs is dependent on the rate of transmission over the blood-brain barrier, the rate of breakdown and retention within the brain, and the combined take-up and detachment rates in the various brain areas.



¹ SPECT and PET scans do not show actual dopamine levels: it is suspected that they measure short-term (within a few hours after the dose) dopamine transport activity at certain dopamine receptor sites. You might say that they measure receptor responsiveness, rather than dopamine. The fact that these scans show a decrease in dopamine receptors in PDers is actually further proof that it is not just dopamine, but the entire dopamine system that is being compromised in Parkinson's. (This subject is beyond the scope of this book.) SPECT and PET scans cannot show existing dopamine quantities nor can they measure the relative changes in native DA levels that may occur after weeks or months of dopamine administration. At this point in time, a radiological study of dopamine receptor activity is not able to detect a long-term change in dopamine accumulations in the limbic area.

HYPOTHESIS 2 – DRUG ACCUMULATION

The idea that dopamine can accumulate over months may seem old to you by now, after having read about Build Ups, Daily Deficits, and drug reduction cycles. However, in the world of western medicine, this is a very new idea and constitutes our second hypothesis. We feel that the hundreds of charts of those patients in which dopamine dose effects were clearly being influenced by drugs taken on preceding days, as was demonstrated by the small sampling of Sonny's charts shown in this chapter, supports this hypothesis.

Dopamine-enhancing drugs may accumulate in the brain over the course of a day, so that the drugs of any given day have an additive effect. Dopamine in the limbic area may accumulate or decline over a ten-week period, so that a response to drugs taken (or not taken) on any given day may be affected by drugs taken (or not taken) up to ten weeks earlier.



HYPOTHESIS 3 – CHANGING ADDICTABILITY

PDers are much less addictable than average but a recovering PDer has normal susceptibility to addiction.

The bizarre cases of Zoe, Viktor, Birdie, Coach, Euclid, and Brad, all of whom you will meet over the course of this book,¹ pointed towards this unanticipated conclusion. At least for this third hypothesis, there was no existing, contradictory theory that we had to overcome: no one had even given any thought to the issue!

Our first suspicion that PDers were addiction-resistant was based on the responses our patients gave when we discussed addiction. Fairly early in our program we started warning patients that we suspected their drugs might be addictive. We were stunned by the uniformity of their response: patient after patient told us that they, alone among their friends, had never had any trouble when quitting any addictive substance. Their experiences with addictive drugs ranged from alcohol and cigarettes to cocaine and heroin, and yet none of them, to hear them tell it, had any real problem stopping the drugs.

¹ And this group includes ten others whose cases would be redundant and who have not been included due to space considerations.

A smoke screen

Maybe the best way to convey the significance of this uniformity is to share an unintentionally humorous research report that related Parkinson's disease and cigarette smoking.

A long-term, general survey of the lifestyles and habits of thousands of men showed that only half as many men with Parkinson's were smokers as would be expected, given the percentage of smokers in the general population. The naïve conclusion stated that, therefore, smoking cigarettes possibly prevented Parkinson's disease!¹

Curious about this finding, I discussed the matter with my patients. Many of my older patients told me that, back in the days when smoking was considered beneficial, they had been smokers. Some of them had even taken up the habit at their doctor's suggestion. (In the 1950's, cigarettes were considered a tonic for the nervous system and were widely recommended by physicians.)

None of these patients were still smoking. In the 1970's and 1980's, when the news was coming in that cigarettes were harmful, my "smoker" patients had simply stopped smoking. None of them had any problem quitting. When they were told that cigarettes were good, they had smoked. When they were told that cigarettes were not good, they quit. The fact that fewer people with Parkinson's smoke cigarettes may have much to do with their extreme desire to do what is correct and to avoid what is harmful, aided by their pathological level of self-control. But it may also be related to their decreased susceptibility to addiction.

The researchers in the survey had most likely confused cause and effect – a common error. Because many PDers don't smoke, they had leaped to the conclusion that smoking prevents PD. Instead, it might have been most accurate to say that people with overt or latent Parkinson's disease do not become addicted to cigarettes. Whether they choose to smoke or not may depend on the advice they have been given about health-related issues. Whether they quit or not may simply depend on whether or not they have decided, for whatever reason, to simply stop smoking. The issue of addiction, normally the big stumbling block to quitting smoking, was apparently not a problem with my PD patients.

When queried as to the difficulty of quitting cigarettes, all of my patients made some remark such as, "It wasn't a problem, I just did it," or simply repeated the ironic mantra of so many people with Parkinson's disease, "Mind over Matter."

¹ This delightful conclusion was actually published and received quite a bit of press. (D. Morens (University of Hawaii), *Neurology*, June, 1995.) I use this study as a teaching tool: an example of faulty logic. A study about coffee, also done by the University of Hawaii, was actually published in the *Journal of the American Medical Association*. (See A. Nehlig, "Association of coffee and caffeine intake with the risk of Parkinson's disease," *JAMA*, 2000, May 24-31; 283(20): 2647-9.) This study proposed that drinking coffee prevented Parkinson's, because most PDers did not imbibe java. I wrote to the *JAMA*, pointing out that many of my patients had enjoyed coffee at some point in their lives, but that as their internal agitation increased to the point of internal, and then external, shaking, the last thing they needed or wanted was something that would jangle their nerves even further. Considering that most of them were over the top with adrenaline, coffee, a stimulant, was not on their "must have" list. The *JAMA* wrote back and asked if they might print my response. I said yes and indicated with my initials that I was an acupuncturist, not an MD. I did not hear from them again, nor was my response published, to my knowledge.

I have since met PDers who do smoke or drink coffee; they often do it ritualistically rather than obsessively, such as relaxing into a pensive cigarette at the end of the workday. They do not need an ever-increasing amount of cigarettes over the weeks and years to sustain the mildly pleasant effect of the nicotine – one cigarette will suffice: they are not physiologically addicted; they are merely habituated.

With other patients who had overcome drinking problems or cocaine abuse, it was always the same story: “Quitting wasn’t a problem,” or “I just put my mind to it, decided to quit, and I was done with it.”

Their dangerous corollary was that reducing Parkinson’s drugs would not be a problem either. They assumed they could apply the same cool, focused will power to getting off the PD drugs as they had used on other addictive substances. Though lesser people might struggle, the PDers – with their superior focus and stick-to-it-iveness – knew they would win through.

As patient after patient expressed this haughty attitude, based on their experiences with wine, tobacco, or drugs, it was borne in on us that we might be seeing something that had never before been studied. It appeared as if most people with idiopathic Parkinson’s disease (not drug-induced parkinsonism), people with unexplained low dopamine levels, were less susceptible to addiction than was the general public. There were other puzzling aspects to their relationship with dopamine and addiction, as well.

We listed the following observations:

- 1) Our PDers often had a history of easily overcoming otherwise addictive substances – or so they said.
- 2) According to their accounting, if the PDers had used addictive substances, they had not needed to use ever-increasing amounts to obtain the desired result.
- 3) Our PDers, *even when overmedicated*, and therefore having an excess of dopamine, as evidenced by dyskinesias, did not appear to become *quickly* addicted nor did they need to increase medication quickly, but could usually stay at any given drug level for up to six months before the drugs waned in effectiveness. Also, if they needed to stop taking the drugs for a day or two, they could usually do so without slipping into impassioned cravings.
- 4) We compared #3 (above) with the fact that highly addictive drugs – in most people – may decrease in effectiveness within a matter of weeks, or even days. Also, cravings for addictive substances can develop quickly, depending on the drug.
- 5) When people in our Parkinson’s Recovery Project began to feel calmer inside and more capable of expressing emotions (as recovery from Parkinson’s disease starts up, emotional changes may occur before any physical improvements begin to manifest), their medication sometimes became dramatically more effective, almost overnight. Dyskinesia rates soared. And yet, very often, within as little as 72 hours, these patients expressed a sudden, powerful desire to *increase* their medication.
- 6) If they continued taking medication after this point, they often had an abrupt turnaround in their goals: they often wanted to quit our program, refrain from contact with former health practitioners, and – most especially – not talk to anyone about medication. They often appeared illogical and/or became extremely defensive and/or secretive about their medications. On the other

hand, some became insanely proud of their new blissful, tireless condition, showing off for friends and neighbors, and wanting to convert us to the School of Infinite Dopamine.

- 7) When our patients decreased their medication in advance of experiencing symptoms indicative of recovery from Parkinson's, they experienced poorer drug coverage for their symptoms, as expected. But after completing a reduction cycle, their lowered drug doses yielded the same symptom coverage that they had before with the higher drug levels – if they were still taking more than a small, “minimal” amount. On the other hand, if they had not yet recovered and reduced their drugs to a level below the minimum needed to mask Parkinson's, their PD symptoms would be exposed and remain exposed even at the end of a reduction cycle. This minimum level is detailed in chapter 17 (The last little bit). Whether or not their PD symptoms improved back up to the prior (pre-reduction) level at the end of a cycle seemed to depend on whether or not they were taking medications higher than a minimum level. This minimum was much lower than the manufacturers' recommended dosages.
- 8) Those few patients who did try to reduce medication after exhibiting, for more than 72 hours, symptoms consistent with recovery plus overmedication usually underwent the extreme rigors of classic drug withdrawal. These rigors might include nausea, extremes of insomnia, paranoia, violence, hallucinations, and life-threatening heart or diaphragm arrhythmias. These violent symptoms often lasted ten weeks before they showed any sign of fading. Subsequent drug reductions, if not undertaken immediately after the withdrawal began to ebb, might also repeat this pattern.

Based on these observations, we made the hypothesis and corollary that people with Parkinson's disease are less susceptible to addiction than the general population and people who recover from PD will be more susceptible to addiction than they were before.

We had to look long and hard at the most curious piece of information – item number 3, above. The people referred to in this section had dopamine at levels that were causing their bodies to go into spasm. They clearly had more dopamine than was necessary. They were over the Safety Limit. And yet, they did not behave as if they were particularly addicted. They could often stay at a high, dyskinetic medication level for a long time – some of my patients had been ticcing and thrashing about at the same drug levels for more than a year – without needing an increase. Although overmedicated PDers do eventually have a lowering of their baseline dopamine in response to excessive drugs, it seems that this happens so much more slowly than addiction in healthy people that it can be considered negligible in the short term.

So, despite the most recent research coming from the drug addiction community, which pointed to excess dopamine being the crucial factor in drug addiction, we were seeing that there was something beyond merely the dopamine that was involved.

Also, although those people in situation number 3 above were clearly overmedicated, according to the obvious dyskinesias, if they tried to reduce their medication *before* they started having signs of recovery, they did not undergo drug withdrawal symptoms, but merely suffered from the usual signs of drug decrease: an

extreme decrease in the masking of their Parkinson's disease symptoms which corrected within ten weeks. These decreases did not leave people shell-shocked or traumatized. Following a drug decrease, this group would be merely miserable, possibly immobile, and often in severe pain, but usually after about ten weeks, depending on whether or not their drug levels had been over the minimum, they were having their prior level of movement again, with fewer adverse effects from the drugs.

Many people in the program did begin to reduce their medication prior to seeing any hint of recovery; they initiated the reductions when they learned that their adverse effects were, most likely, coming from their drugs and not from their PD. Many people found that, regardless of recovery issues, they eventually felt much better with much less medication. As described earlier, some of them had tried reducing their drugs in the past, but, because they did not understand the ten-week time frame for brain readjustment, they had assumed after two to ten days at a lower level that they had been wrong to reduce. Armed with more information about how addictive drugs work, and the time frames involved, many patients tried anew to reduce their drugs after entering our program, with beneficial results. And – despite being clearly over the top with dopamine – they did not experience the traumas of drug withdrawal (addiction) if they were not yet manifesting *any*, however subtle, symptoms of recovery.

A person with Parkinson's disease has reduced susceptibility to addiction.

Upon beginning to recover from Parkinson's disease, he will immediately be just as susceptible to addiction as any healthy person.

Medication that was merely somewhat addictive during the PD condition may become rapidly and irreversibly addictive in even very small amounts after recovery begins.



HYPOTHESIS 4 – A SEE-SAW RELATIONSHIP BETWEEN ADRENALINE AND DOPAMINE

Addiction is more likely when the body is in a parasympathetic condition than when in a sympathetic condition.

We created a new hypothesis to explain the normal = addictable versus PD = addiction-resistant hypothesis already stated.

Hypothesis 4 is necessary to explain PDers being overmedicated, oversaturated with dopamine, but not being addicted. If dopamine alone were the sole cause of addiction, as currently hypothesized by the National Institute on Drug Abuse, then these overmedicated patients should have been horribly addicted – but they were not.

This idea has immediate bearing on medication issues. However, in understanding the overall Parkinson's picture, this hypothesis is even more crucial – it is connected to

our realization that Parkinson's disease occurs when the body is locked into a sympathetic system and that recovery begins when the parasympathetic system is reinstated.

The myriad symptoms of Parkinson's, including the decrease in dopamine producing cells over the decades, are merely side effects of this injury-induced sympathetic condition. The fixation that some recovering patients in our program have with finding all their past injuries and blockages that might have contributed to the erratic electrical flow in Parkinson's is, in fact, off the mark. The key factor is returning to a state of relaxation after a lifetime of wariness. Very often, the treatment we provide, which supports the injured areas, allows a PDer to have the emotional recognition of injury, after which he can defuse the sympathetic system. The treatment of the injury and the shutting down of the emergency often go hand in hand. But actually, it was the fearful sense of emergency rather than the injury per se that prevented the injury from healing normally at the time of occurrence.

This idea is the core of our work, and it is supported, in part, by what we saw while working with drugged patients.

Adrenaline vs. dopamine

We propose that a person who is in a condition of sympathetic nervous stimulation will have a body-wide increase in adrenergic function and a corresponding decrease in all dopaminergic functions. This decrease in dopaminergic function applies to the production, transport, reception, and breakdown of dopamine, as well as the addiction response to dopamine. During the sympathetic condition, all brain processes, including motor function, alertness, emotion, and memory, switch from a dopamine-based system to an adrenergic system. While under the influence of the adrenergic system, all dopamine-based systems, including dopamine-induced movement, thoughts, and the addiction response to dopamine are greatly reduced.

Dopamine has helpers

We suspect that the actual molecule of dopamine does not perform all of the neurotransmission that occurs in the dopamine-dominant state. An entire cascade of neurotransmitters can be called into play by either the adrenaline or the dopamine team captains. However, for our purposes, we are going to focus on the two chief NTs of the systems rather than on the torrents of subordinate neurotransmitters. It may be that even the hormonal systems, long considered to be glandular, and therefore falsely thought to be separate from neurotransmitter function, are regulated by these two systems. This would explain why the hormone systems do not function normally in times of high stress; maybe most of the hormones are on the dopamine team.

Dopamine: good for what ails ya

Although most people in western society who have been diagnosed with Parkinson's are directed to focus on the amount of dopamine that they can force onto a brain that is trying to not use dopamine, we are guessing that their real problem lies with every aspect of the dopamine system being turned off, not just the quantity of dopamine available. For those who would counter with the specious argument that declining dopamine levels alone make the Parkinson's apparent, based on the glorious "reversal" of

symptoms when a PDer takes levodopa, I would propose that levodopa at those high levels would make just about anyone feel better, move better, and even dance better, whether they were suffering from chicken pox, a broken leg, or Parkinson's disease.¹

It is not just a recent dopamine deficiency that is causing Parkinson's disease; most PDers haven't used dopamine in decades and wouldn't know what native dopamine felt like if it bit them in the ankle. The reason that Parkinson's becomes apparent is that the adrenal system, due to a shock, illness, surgery, or exhaustion, begins to be inadequate.

It is the worsening insufficiency of this dynamo, the adrenal system, also known as the sympathetic system, that finally allows the damage from years of irregular electrical patterns – *which includes long-term dormancy in the dopamine-producing cells* – to finally be exposed. The problems of damaged muscle tissue, the disconnected sensory nerves, and the sleeping dopamine branch of motor command centers in the brain have been snowballing for years, concealed in the blizzard of adrenaline. By being in a state of emergency, the PDer has been able to ignore these problems and override them.

PDers can move in an emergency

It is well known that, during the first decade or so after a diagnosis of Parkinson's, an otherwise immobile person can still, when confronted with an extreme emergency, move perfectly normally. In other words, if the wearied adrenal system can be encouraged to rev itself up for a short time, a person can feel exactly like his or her old, dynamic (sub-clinical Parkinson's) self again. As soon as the emergency diminishes, however, the adrenal system slumps back down, exhausted after so many decades of working overtime. Once the emergency is over and the sympathetic system subsides again to an inadequate level, the underlying decay in the body from backwards flowing electrical circuits, the rigidity, poor balance, and inner restlessness/fear are all once again apparent. This decay, falsely attributed to dopamine decrease, is actually the normal consequence of injuries that have failed to heal. The body does not do healing work while in the sympathetic state.

Two separate sets of neurons

Much study has been done on the sympathetic system, but the parasympathetic, falling under the large heading of "Normal," or "default system," has been relatively unstudied. It has been known for nearly a hundred years that adrenaline (epinephrine in England) is the neurotransmitter for emergency, regulating all emergency systems, ranging from the heart, bladder, lungs and blood vessels to the very way in which we

¹ Due to deeply depressed dopamine levels and having an autonomic nervous system locked into a permanent, even though depleted, extreme sympathetic mode, people recently diagnosed with idiopathic Parkinson's often have slow response to the antiparkinson's drugs, requiring several weeks or even months on low level antiparkinson's therapy before they begin to notice the result. Many of my classic, idiopathic Parkinson's patients say that they took L-dopa for only a month and quit because they didn't notice much of an effect.

On the other hand, quick, buoyant results from antiparkinson's drugs can sometimes signify misdiagnosis. Recent research (see footnote, p. 159) shows that misdiagnosed patients often notice a dramatic, quick effect, and rapidly begin manifesting addictive behaviors, in addition to feeling just *great* from the medication no matter what their particular problem was. This is particularly ironic because, starting in the 1990's, undereducated MDs began using rapid response to L-dopa as a positive indication of idiopathic Parkinson's.

think and process information. Adrenaline causes a shift in the brain's speed and method of learning.

We have seen events during recoveries from Parkinson's that have directed us to the following new idea:

The neurons (nerves inside the brain) that stimulate muscles, regulate coordination, and integrate left and right brain sides respond so differently to adrenaline than they do to dopamine that there may be *an entirely different set of neurons* used during emergencies. A person may have two distinct sets of physical skills, thinking patterns, perceptions of time, and personalities: one set is run by adrenaline, the other by dopamine. The addiction process is a part of the dopamine-regulated system. The addiction process is dormant, or somewhat modified, when the adrenaline system is dominant.

The existence of two separate systems would explain why, during recovery from Parkinson's, our patients sometimes must relearn coordination for activities that they had mastered during their years on adrenaline, and which they could perform up until they started to recover. Very often, it is as if they have never done the activity before. These activities can range from typing and tying their shoes to reading poetry.

Very often, a recovering PDer feels as if the brain has no way to remember ever having done these activities.¹ This can be combined with sudden bursts of long-forgotten movements that bring to mind memories of childhood: "I just ran my violin bow over the strings and the music came out in the effortless way it did when I was a youth. It wasn't just the physical motion that was different; it was as if the source of the motion, the freed emotion behind it, the fluidity from deep inside – it was all there, all at once. I can remember that that was the way I played the violin long ago. I don't know when I stopped doing it that way. I feel as if I've been trying to recreate that feeling in the bow ever since I was about twenty years old. Suddenly, yesterday, it all came flooding back!"

For activities that were learned subsequent to the injuries that cemented the emergency condition, it can feel as if one is doing the activities for the first time. This could be explained by the existence of two distinct sets of brain responses, which may be only partially integrated.

Just as we now accept that adrenaline runs an entire galaxy of symptoms and commands a phalanx of neurotransmitters, it may be that dopamine runs a separate, parallel, physiological galaxy, equally armed.

This idea is actually more significant to biology in general than any of the other hypotheses. These ideas came to us while observing what happens during recovery from Parkinson's. It was the dramatic brain shift in recovering patients that brought us to this point. Before I can write another word, I take a moment to once again bow to those patients, both medicated and unmedicated, whose brave experiments have brought us to this new understanding.²

¹ See: "panic attacks" in *Recovery from Parkinson's Disease, A Patient's Handbook*, J. Walton-Hadlock. Free at www.pdrecovery.org.

² While this hypothesis does not give particular help to a person who is trying to make sense of his medications, the biologist in me is equally fascinated by this new way of viewing the parasympathetic system, a system I first learned about more than thirty five years ago. If I can make a contribution to our understanding of this system, I dedicate this contribution to my beloved biology professors, especially Mr. Campbell and Miss MacDonald (Santa Monica High School), and my mentor, the late Dr. Kenneth V. Thimann, professor emeritus, University of California, Santa Cruz.

Quick transitions

Another proposal, one that fits in with the above hypothesis, is that the body is capable of moving very quickly between the sympathetic-dominant and parasympathetic-dominant states. The deeper, emotion-based changes that we saw in our patients when they began to recover often occurred within a matter of hours after a breakthrough treatment. The ensuing drug addiction, if they were medicated, might be full blown within three days. Evidently, the switch that allows the body to go back and forth between heightened alertness and normal, between addiction-resistant and addictable, is a quick one.

A graduated scale, rather than an On-Off switch

Although, to make the point, I presented the adrenal versus dopamine systems as one or the other, all-or-nothing, it is more likely that the toggle between sympathetic and parasympathetic is not so much a one-or-the-other switch, but a graduated line.¹ Both systems are ordinarily somewhat active at the same time. When one system predominates, the other decreases. This gradual back and forth, with one system or the other dominant, but both systems active to some extent, allows for healthy people to experience appropriate levels of responses in times of ease and times of concern.

When the adrenaline system is dominant, the dopamine functions are turned down to a very low setting, and vice versa.

Sick people, however, such as those with Parkinson's, those who are in extreme pain, and those who are in a state of constant, unending emergency, may find certain aspects of their dopamine system are turned so low that they are, for all intents and purposes, turned off. This would explain why people in these conditions have almost no addiction response. However, the dopamine system is obviously able to spring back into effect in its entirety as soon as the emergency is removed – even after years of “emergency.”

Interestingly, it appears that, in such a case, when dopamine resumes after an unhealthy long period of adrenal hyper vigilance, the adrenal system will give itself a nap and not be rousable by any but the most dire of emergencies. This condition exists in recovering PDer's who find that nothing short of calamity can stimulate them into a condition of even mild concern anymore.

¹ This idea is developed further in a lengthy footnote in chapter 24.

Further support for our hypothesis

Our hypothesis is helped along by two findings: a change in social status in a primate/addiction study caused a change in both dopamine receptor activity and addictability, and people in extreme pain are less addictable. (See Appendix 7.)

Alpha primates

The sympathetic system in male primates who become alphas may increase due to heightened wariness against challengers and natural enemies. This finding appears to be related to what happens in PDers. (See Appendix 7.)

Pain

People who are in extreme pain, such as post-surgery, may not need regularly to increase their dose of otherwise addictive pain meds in the usual manner of addiction. When their pain later subsides, they can usually stop or decrease their drugs without cravings or drug withdrawal if they stop their drugs in a timely manner. The extreme pain may have triggered the sympathetic system, turning off the addictable parasympathetic.

More on monkeys

Research using cocaine (see appendix 7) has shown that previously addictable primates are no longer addictable after becoming an alpha (leader of the group). What else changes when a primate becomes recognized as the alpha male of his group? A primate that becomes an alpha male takes on responsibility for the safety of the entire clan. He must be awake when others sleep.

He also faces challenges from within his community. He needs not just superior strength but superior cunning and the ability to psychologically keep his potential challengers at bay. He must maintain a heightened sense of alertness. He must be forever watching over his shoulder and may never let his guard down. A single slip up and an entire pack of challengers might be at his throat.

To perform his duties and maintain his position, he must sustain heightened vigilance. He may not slip into a parasympathetic mode – in such a relaxed condition he would soon change species: from an alpha chimp to a sitting duck.

PDers as alphas

Some PDers manifest their extraordinary ability for self-control by being supremely submissive. Some use their unnatural levels of self-control to subtly manipulate or even dominate others. However they choose to use their enhanced state of alertness, intelligence, and speed – all conditions brought about because they are in a state of injury – they are still in a “sympathetic” condition, biologically speaking.

While the sympathetic system is often understood to be a condition of emergency, and is oversimplified for beginning biology students as a condition of “fight or flight,” the condition is more complex than mere running or attacking: enhanced mental and diminished emotional/contemplative capability also accompany activation of the sympathetic nervous system.

Enhanced emotional and physical wariness and a tendency to be “stronger, faster, and smarter” than normal people are common attributes of the Parkinson’s personality. They also neatly describe the behavior of an alpha primate.

More on pain

In looking around for any sort of comparison with the non-PD community, we have considered the non-addictiveness of people who are in high levels of pain, but who, when the pain is over, return to a perfectly normal level of addictability. Stories are common about those people who abuse pain medication after they are released from hospital and end up becoming addicted: after their pain has receded – if they are still using pain meds – they need ever-increasing doses and their lives revolve around their drug addiction.

However, it is also recognized that some people who are in extreme pain can tolerate extremely high levels of dopamine-enhancing drugs without becoming addled by them, yearning for them, or needing ever-increasing doses. The difference seems to be that people who are in a state of excruciating pain (pain causing a sympathetic system response which includes an extreme dopamine deficiency and/or dopamine override in the limbic area) are not addictable. But I repeat, as soon as the emergency-level pain subsides and becomes background level pain, they are again addictable.

The image of fight or flight

Most people have been taught that adrenaline is the “fight or flight” chemical. The image of a charging rhino is often used to demonstrate what triggers the sympathetic response. But extreme pain, or the perilous potentialities of being an alpha male, can also set the sympathetic system in action. We propose that certain emotional or physiological terrors, and the subsequent perpetual wariness, can also perform this function. This is the most common sympathetic system trigger for PDers. After the sympathetic system is elevated, dopamine levels – and the entire dopamine system, including healing functions and addictability – drop very low.

Why medicated PDers should not attempt recovery

Recovering PDers have almost no sympathetic nervous system. They appear to drop to an almost pathological parasympathetic mode during recovery, during which they virtually cannot be stimulated into an emergency state.¹ We have to wonder if a commonality in recovering PDers and ex-emergency patients (those who have emerged from their crisis) is an overswing into an extreme parasympathetic mode after having been in an extreme sympathetic mode. This change, not dopamine levels per se, may be the reason for ex-PDers and some previously pained patients switching over to an extraordinarily high level of addictability from a previous condition of non- or minimal-addictability.

For purposes of healing PDers, we usually focus on their unhealed injury or, often, multiple injuries. It is the chaotic electrical pattern in the vicinity of their injury that eventually creates the various symptoms of Parkinson’s disease. However, the real

¹ Please read J. Walton-Hadlock, *Recovering from Parkinson’s Disease: A Patient’s Handbook*, available for free at www.pdrecovery.org.

problem has never been the injury. The deeper level problem is that, because the person was in a state of (very often emotional) emergency at the time the injury occurred, the injury did not commence healing. *When a person is in a predominantly sympathetic state*, whether he is conscious of emergency or not, whether using his adrenaline and altered awareness to appear either utterly meek to the point of invisibility or completely ferocious, he cannot heal from injury; nor, we propose, can he become addicted.

What actually allows the healing of Parkinson's to occur is the singular method that we use for healing: we hold the patient's foot. We, the health practitioner, assume a posture towards the patient that has signified, through time immemorial, that the person whose foot is being held can let down his guard and be at peace. The emotional implications of allowing one's foot to be supported, of letting a foot be held peacefully by a neutral fellow human in a safe setting, may provide a signal, long-denied, that the emergency is over. (Fully developing this idea, that the PDer was in a state of emergency, is beyond the scope of this book.¹)

However, if recovery will cause a PDer to revert to the parasympathetic state, the risk of taking antiparkinson's drugs – some of the most addictive drugs known to man – while trying to recover, is apparent.

One of the gravest problems with medicated people trying to recover from Parkinson's is that it may take years for the body to return to full strength. The lingering weakness and slow muscle retraining make it extremely difficult for a PDer to relinquish his medications. And yet, we have seen over and over that, as soon as the person turns off his protective, sympathetic stance so that the electrical disarray can be reconfigured, he is at great risk of becoming addicted to his medications. It has been known since 1969 that these drugs are neither safe nor stable at any level in a non-PDer. You begin to see where the danger lurks in treating a medicated patient.

A patient's extreme level of immobility due to the muscle damage incurred during the decades of Parkinson's may take years to repair. Massive doses of dopamine, such as those used in treating Parkinson's, can provide an emotional high that allows movement despite his technical immobility.

As an example of "being able to move even though technically immobile," let me use a person with a broken leg who, under normal circumstances, is completely unable to support weight with that broken leg. Given enough cocaine or methamphetamine, this person may move about quite happily. He may be shredding his leg inside, further damaging the injured bone and doing himself a great mischief by dancing about with a broken leg, but he can do it, nevertheless.

The dopamine-enhancing drugs impart movement to a PDer in very much the same way. They give the possibility of mobility and the illusion of health in a person who, physiologically, would be better off immobile.

The temptation to continue using the drugs even though the dopamine system has switched back on is so alluring that most people succumb. Their previous years of "iron will" are of no use to them now. Their will power was a part of their training under their sympathetic system, a system which shuts down during recovery. If these drugs are taken when the dopamine system has turned back on, rapid addiction and all the side effects of

¹ Please read J. Walton-Hadlock, *Recovering from Parkinson's Disease: A Practitioner's Handbook*, available for free at www.pdrecovery.org.

addiction – pain, delirium, and permanent brain damage – including parkinsonism – can ensue.

Because of the irreversibility of the brain damage that might occur when a person is, however briefly, addicted, we do not recommend recovery from Parkinson's disease for any person who is taking antiparkinson's medications.

Summary of hypothesis four

The sympathetic system is governed by adrenaline *and the parasympathetic is regulated by dopamine.*

Addiction is a parasympathetic process.

Resistance to addiction occurs during a heightened sympathetic response.

When in a parasympathetic state, addiction will occur in response to excess dopamine.



Summary

1. The effective duration of all dopamine-enhancing drugs is dependent on the rate of transmission over the blood-brain barrier, the rate of breakdown and retention within the brain, and the combined take-up and detachment rates in the various brain areas.

2. Dopamine-enhancing drugs may accumulate in the brain over the course of a day, so that the drugs of any given day have an additive effect. They may also accumulate or decline over a ten-week period, so that a response to drugs taken or not taken on any given day may be affected by drugs taken or not taken up to ten weeks earlier.

3. Most PDers are much less addictable than average but a recovering PDer may rapidly return to a normal susceptibility to addiction. Medication that was merely somewhat addictive during the PD condition may become rapidly and irreversibly addictive in even very small amounts immediately after recovery begins.

4. The sympathetic system is governed by adrenaline and the parasympathetic is regulated by dopamine. Addiction is a parasympathetic process. Resistance to addiction occurs during a heightened sympathetic response. When in a parasympathetic state, addiction will occur in response to excess dopamine.