

## Appendix 5

# WHY YOUR DOCTOR THINKS WHAT HE DOES:

## FIFTY YEARS OF CHANGING DOPAMINE THEORIES

### *Why read a history of dopamine?*

One of the most difficult challenges for people with Parkinson's disease can be daring to disagree with the medical/scientific world. The same unquestioning reverence that was once given to high priests is now, in these modern times, sometimes accorded to medical doctors. Despite the constant changes in medical theories, doctor knowledge is, to some, High Knowledge. Even though there can be scant conformity of medical theory from one USA MD to another on certain issues, patients can have emotional reluctance to breaking through the "white coat barrier" and thinking independently about their health issues. And yet, so-called Scientific Facts cherished by one doctor may be laughable history or radical unsupported nonsense to another doctor. Still, most non-medical US citizens turn to their MD when they want "the answers."

When PDers realize that they must find their own way amongst conflicting medical theories, they often are confronted with hostile opposition from family members who have blind allegiance to anyone wearing a stethoscope. The inner-family conflicts about the right medical course to pursue when a loved one is diagnosed with an "incurable" illness can be as painful as religious schisms. Therefore, to muddy the waters further still, this appendix will give a quick history of the science of dopamine to explain how the current medical conflicts of opinion arose.

### *Medical differences of opinion*

Many of my patients unfairly expect their doctors to be up to date with the rapidly changing theories of medicine, pharmaceuticals, and chemistry. It is impossible for a clinical (working with patients) doctor to keep up with the crush of new information, much of which is in full opposite, 180° conflict with the theories that he was taught in school. For an example, this education gap leads to our current medical schisms in which some neurologists proclaim that PD drugs are safe and others warn that the drugs are dangerous. Some older neurologists insist that levodopa is the best drug and some of the youngest doctors point to the agonists as the only sensible choice. A few neurologists still tout Eldepryl! Based on our close experiences with the prescribing patterns and the reactions to new ideas of over thirty neurologists, and our long distance experiences via emails regarding prescribing patterns and opinions of hundreds of others, it appears that the weightiest factor in determining a neurologist's opinion about the drugs is this: those drug trends that were popular in the year the doctor graduated from med school. Despite continuing education courses that tout the newest theories and hypotheses, what a doctor learned in med school is most likely to remain as his body of "facts" against which all new information will be warily judged.

### ***Changing facts – a personal confrontation***

The history of dopamine provides a nice example of the way in which science anoints mere conjecture as solid fact and then, as these “facts” are found false, creates convoluted logic in a desperate attempt to keep the “facts” from becoming laughing stocks.

In 1998 I was personally involved in the quagmire of false dopamine information. When I tried to publish my first research article – which included as a sidelight an explanation of the electrical circuitry that causes brain dopamine to be abundant when one is awake and to diminish during sleep – the editor balked at printing that small, awake/asleep dopamine-related portion of the paper. At that time, the facts about daytime/nighttime dopamine were the exact opposite of my finding, and had been for over forty years. As an aside, right now, a mere six years later, the scientific research community has done an about face on the dopamine awake/asleep issue, reversing their earlier, “scientific” fact by 180°. Still, for the most part, doctors who went to school prior to 1998 are still adamant adherents to the old dopamine at night “fact” even though teenagers now learn the new, opposite “fact” in high school biology classes.

### ***Respecting the past***

It is difficult to write about the history of science without sounding smug. It’s easy to smirk at the past, but, though gratifying, it’s not actually productive to say, “Look how stupid our ancestors were! We are so much smarter now.” The one lesson that history of science has to offer us is that every generation has laughed at the preceding one, and that those scoffers were in turn found to be fools and simpletons by the next generations of truth holders. We have to assume that we are in the same situation; today’s science is going to look pretty shabby in another fifty years; most of today’s facts will be proven to be glaring falsehoods, most of today’s medicine – like last year’s medicine – will soon be proven to have been worthless, if not damaging.

The following pages show that the ideas about dopamine have taken a major shift every ten years. The ideas to which your doctor probably adheres will probably depend on which decade he attended school. Note the date on some of the outmoded dopamine research; you may be surprised at how recent some of the now outmoded theories are. For fun, figure which era’s dopamine theory corresponds to the year that your neurologist probably graduated from med school. For a real eye opener, calculate what the age of your neurologist’s *teachers* might have been when they, the teachers, were in school. You will realize that your neurologist may have been instructed by professors who did their own college learning prior to the discovery of dopamine!<sup>1</sup>

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<sup>1</sup> Do not imagine for a moment that a professor is necessarily up to date. In 2001 one of my students attended a lecture given by an older Harvard psychologist who explained that “the brain is like a switchboard; pathologies are caused by incorrect hook-ups.” This idea, popular in the 1950’s, is utterly outmoded.

The current (and subject to change) model of the brain is one of an ever-changing mass of interrelated components. The chemicals in the brain create minute electrical fields, and the larger electrical fields running along the neurons alter the shapes of the brain chemicals. Even the molecules themselves have been shown to shapeshift, so that a molecule with a particular role can change its three dimensional shape without actually changing its atomic components, and can, in its new shape, perform a completely different function than it performed in its previous shape. (Footnote continued on next page.)

Very few doctors have the time to keep up with changing theory; they are lucky if they can keep up with the new medication ads in the Sunday newspaper supplement and the changing legal requirements of practicing medicine in a litigious society.

To enable the modern PDer to compassionately understand why his doctor thinks the way that he does about Parkinson's disease and dopamine, even though that doctor may be in conflict with the latest research, I am presenting this appendix on the history of dopamine theory and how it relates to the underlying philosophy of modern science. Biology research is only slowly reflected in medical changes. For example, many of the long-*disproven* theories of biology that you will read about below are still used today, decades after having been disproven, as the basis for drug treatments. Not only that, but it is not uncommon for doctors, *especially* the top doctors and leaders in their field, to still subscribe to old knowledge that has long since been proved wrong; they are often the ones who, in their early research days, discovered the now-outdated information, and they will very often fight until their death against the newer findings. Also, money is at stake; research grants most often support building upon previous research; even when the old information has been proven to be outmoded, the research grants are still more likely to go to someone experienced, someone who has established his reputation by creating the old theories and who, coincidentally, has a vested interest in fighting against the new changes.

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It now appears that biological molecules can change their shape in response to changes in their cellular and extracellular environment. And yet, the crude idea of brain as switchboard is still being expounded by hoary profs!

The brain, once thought to be a static mass of unchangeable cells, is now held to be ever changing. The brain of ten minutes ago has been irrevocably altered by the events of the last ten minutes. In the time you have spent reading this book, your brain has already altered to accommodate what you've read, what you've eaten today, and the good and bad news you've heard on the radio. You truly do not have now the same brain that you had when you started reading this book. Not only that, but the way in which the brain integrates new information may be random!

In contrast to the static switchboard model still being taught today by some elderly, highly respected PhDs, here is a current (March, 2002) description of the brain: "At a conference of the British Association for the Advancement of Science last fall, neurophysiologists from the University of Cambridge revealed that nerve cells respond to the same stimuli differently every time. 'It seems the brain has a sort of cerebral roulette wheel,' said researcher Roger Carpenter. Randomness may be a valuable survival tool." (Kathy Balog et al, "Heads We Go, Tails We Stay," *USA Weekend*, Santa Cruz Sentinel, March 1-3, 2002.)

A powerful condemnation of the 19<sup>th</sup> century "clockwork" approach to brain function still revered by some doctors was offered by Arnold Mandell, the San Diego psychiatrist and dynamicist who pioneered the applications of modern (late 20<sup>th</sup> century) scientific theories in physiology. In his dissection and condemnation of overly simplistic, linear, and reductionist methods of regarding the brain, he wrote, "The underlying paradigm remains: one gene → one peptide → one enzyme → one neurotransmitter → one receptor → one animal behavior → one clinical syndrome → one drug → one clinical rating scale. It dominates almost all research and treatment in psychopharmacology. More than 50 neurotransmitters, thousands of cell types, complex electromagnetic phenomenology, and continuous instability based on autonomous activity at all levels, from proteins to the electroencephalogram, – and still the brain is thought of as a chemical point-to-point switchboard."

Gleick, an author in the field of chaos theory, in his commentary on the above statement wrote, "To someone exposed to the world of nonlinear dynamic the response could only be: How naïve." (J. Gleick, *Chaos*, Viking/Penguin, New York, 1987, p. 298-299.)

### ***Sacred tradition***

The science, philosophy, and religion of any given people or age must be synchronous; they must fit hand in hand. The so-called facts of science are actually descriptions of phenomena that have been carefully phrased to coordinate with the politics and religion of the hour. The corollary is that, once a scientific theory becomes established, it is as difficult to change as a cultural or religious tradition. The Parkinson's/dopamine theory is no exception. Before I jump into the dopamine history, let me give an example of how difficult it is to change a medical tradition. I will share this tidbit from a recent Parkinson's disease convention. A respected MD and PhD researcher from Columbia University wrote up the report on which the following section is based.<sup>1</sup>

### ***A disappointing dopamine conference conclusion***

Various papers had been read at the conference, the sixth International Congress of Parkinson's Disease and Movement Disorders, all proving that using dopamine agonists instead of L-dopa as the first course of treatment, or as an adjunct in combination with reduced levels of L-dopa, was much safer, provided better coverage of symptoms, and greatly extended the effective years of the medication (the time period before the drugs developed adverse effects). At the close of the conference, after the reading of all the papers, the doctors in the audience were asked to indicate, by a show of hands, whether or not they would be willing to consider using the safer drugs or modifying their prescriptions of L-dopa, substituting, where possible, the agonist drugs which had been proven, in test after test, to be safer and more effective.

The writer of the article expressed strong dismay as he reported that, surprisingly, even after hearing paper after paper proving that agonists were safer, had fewer side effects, and gave more years of benefit before the adverse effects began, still a majority of doctors in the audience raised hands to indicate preference for continuing to initiate treatment of PD with levodopa – the treatment that had been proven most damaging – rather than start with one of the new agonist drugs.

The author, in his critique of this response, offered up his own suggestions as to why on earth his peers would be so hidebound. He suggested that “[a] possible explanation is that ease of use (some agonists require a much slower titration of dose than levodopa before reaching the same effectiveness)...may play a bigger role in a practicing clinician's choices than the conclusions of a drug study.” He also suggested that habit may play a part. Despite his several possible excuses for his peers' reluctance to change, his writing clearly showed he was both surprised and disappointed in the show of hands; the attendees, for the most part, indicated that doing what was familiar or easier was more significant than doing what had been *proven* to be more effective.

In other words, the majority of doctors who attended a conference to learn the most up-to-date information were not willing to change their methods simply because it had been repeatedly proven that their old methods were dangerous and that better methods had been found. In medicine, as in established religion, it can be just too painful

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<sup>1</sup> Pietro Mazzoni, MD, PhD, “Conference Highlights from the Sixth International Congress of Parkinson's Disease and Movement Disorders.” *Medscape Neurology*, Feb. 2000.

to upset the status quo. The status quo seems to depend on what year the doctor attended medical school.

So let's look at a decade-by-decade quick review of neurotransmitter history. The time frames below refer to discoveries in biology research, *not* to changes in medicine necessarily. The transfer of new information from the realm of biology research into the realm of medicine is notoriously slow.

## A BRIEF HISTORY OF DOPAMINE AND OTHER NEUROTRANSMITTERS

### Pre-1930's

Acetylcholine, a molecule produced by nerve cells, was found to be stored in motor nerve endings. When a motor nerve is stimulated, its acetylcholine supply is released from storage and sloshes across the gap between its parent nerve and the next nerve in the chain. The receptor nerve, stimulated by the presence of acetylcholine at its receiving end, discharges *its* stored portion of acetylcholine from the far end of the nerve. The process continues from one nerve to the next, thus transmitting a nerve stimulation impulse from one nerve to the next. Via acetylcholine, a long chain of nerves can transmit a motor impulse all the way from the brain down to a muscle, where the acetylcholine from the final nerve in the sequence causes the muscle to contract.

The discovery that nerves could communicate their stimulation signals via tiny chemical compounds stunned the physiologists of the day. Since the days of Galvani's electrical experiments with frog legs up until this time it had been assumed that that electricity was solely responsible for nerve signal conduction.

This new type of chemical was named a neurotransmitter. The Nobel prize was awarded in 1936 to Otto Loewi for showing that acetylcholine was indeed a neurotransmitter, a neural chemical communicator. A fun tidbit: the idea for Loewi's prize-winning work came to him in a dream.

The assumption at this time was that there was only one neurotransmitter. Acetylcholine was *it* – end of story. Most of your older doctors will remember their first lab experiments in biology class when they splashed acetylcholine onto frog legs and watched how the legs twitched, jerking back and forth in response to the molecule. But what does this have to do with dopamine?

### 1940's and 1950's

In the 1950's, decades after acetylcholine was discovered, a few other "communicator" chemicals were found to be splashing around in the body, dopamine among them.<sup>1</sup> Dopamine, made in the adrenal gland (just above the kidney), was deemed to be of importance in regulating blood pressure and urinary output. It was used in the treatment of shock.

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<sup>1</sup> Dopamine research started in the mid 1950's. Nicotinic acid (derived from tobacco) was discovered to be a nerve activator (an acetylcholine agonist) in the 1940's, prior to the discovery of dopamine. As late as the 1970's, acetylcholine, dopamine, epinephrine (adrenaline), and serotonin were considered by most biologists to be the only neurotransmitters, or certainly the only ones of any consequence. Actually, norepinephrine and epinephrine were considered for many years to be hormones, not neurotransmitters, because of the association of epinephrine with the adrenal gland.

### ***Nomenclature***

A determination was made that compounds that were made and stored in nerve endings should be called neurotransmitters. The chemicals that were made and stored in glands should be called hormones. Neurotransmitters traveled the merest of distances, from one nerve to an adjacent nerve, and then back again. Glands, on the other hand, could eject chemicals into the bloodstream, whence they could travel throughout the body in search of their particular target organ. Using this new definition, dopamine, which was made in the adrenal gland, was a hormone.

### ***Dopamine, the hormone***

Eventually, dopamine, adrenaline, and norepinephrine presented some labeling problems. Even though they were made in the adrenal gland, they appeared to act on nerves as well as on organs such as the bladder and kidney. This was in conflict with the idea that hormones should act solely on organs. An even greater problem arose when it appeared that brain cells were affected by dopamine. (This research was done on mouse and/or rat brains.) The difficulty was this: dopamine was made in the adrenal glands (down by the kidneys), thus dopamine had an effect on kidney and bladder function, *but* dopamine also affected neurons in the brain. Norepinephrine, also made in the adrenal glands, like dopamine, had an expected effect on nearby kidney function but also seemed to affect the brain. A new description was needed for these compounds that were made in glands, like hormones, and which affected organs but which also affected nerves.

### ***Brain messengers***

A happy solution was settled on. The chemicals that were made in glands but which affected brain neurons were renamed “brain messengers.” This solved the problem, but created a new one. How did a given molecule of dopamine know whether or not it was supposed to be a brain messenger, affecting the brain, or a hormone, affecting organ behaviors? This problem was never resolved, but thousands of college biology majors and pre-meds, this author included, dutifully memorized the terminology. No one knew how or why the chemistry pulled it off, but dopamine was a molecule that performed both as a hormone and brain messenger.

### ***Dopamine and Parkinson’s disease***

By the late 1950’s it was established that the Parkinson’s brain was deficient in dopamine.<sup>1</sup> The mechanism remained unclear. As recently as 1989, the wording in *Taber’s Medical Dictionary* was a vague note that this secondary (brain) role of the brain messenger dopamine was “implicated” in some forms of psychosis and abnormal movement disorders such as Parkinson’s disease.<sup>2</sup>

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<sup>1</sup> I must assume that this was determined using autopsy, the only method available at that time for assaying dopamine levels in the brain. I have not found definitive information on how this deficiency was discovered. Most of the research of this era was done on rats. I suspect that it was probably in rats that the blood-brain barrier’s (BBB’s) impermeability to dopamine was first seen, and also the subsequent discovery of L-dopa’s permeability across the BBB with its subsequent conversion in the brain into dopamine.

<sup>2</sup> *Taber’s Cyclopedic Medical Dictionary*, p. 524.

### ***Failure to respond to dopamine***

Despite the proposed shortage of dopamine in Parkinson's brains, administration of dopamine hydrochloride (a form of dopamine usable by the adrenal gland) to PDers did not seem to benefit Parkinson's patients as anticipated. Therefore, although dopamine was implicated in abnormal movement, the relationship was unclear.

When it was later found that dopamine molecules could not cross the blood-brain barrier, this explained why oral or injected dopamine had not alleviated PD symptoms. (In the early research, as now, confusion about levels of blood dopamine relating to amounts of brain dopamine led to wrong conclusions!)

The finding that dopamine could not cross the blood brain barrier meant that, possibly, dopamine made in the adrenal gland was not a brain messenger at all! Evidently, the dopamine that was used in the brain was actually manufactured in the brain! The brain was made of nerve tissue. If dopamine was generated in the brain, this meant that it was made by nerves, for nerves. It began to appear as if dopamine, with its dual role of hormone and brain messenger, was also a neurotransmitter. The finding that brain dopamine was made in the brain rather than being transported there from the adrenal gland was the beginning of the end of brain messenger theory. (Looking ahead, by 1990, the term "brain messenger," would be hopelessly passé in research circles, but as of this writing, in 2003, some MDs still imagine it to be current.)

### ***Two neurotransmitters***

A larger problem was looming, one that would have consequences for the next forty years of Parkinson's research. New research indicated that dopamine had an effect on motor function: dopamine appeared to have a motor effect when applied to the brains of rodents. This was alarming news. It was established fact that acetylcholine was the neurotransmitter of movement; how could there be two movement neurotransmitters?

A solution was proposed and immediately accepted: acetylcholine caused muscles to tense up; dopamine caused them to relax. This was not based on any research whatsoever – it was pure hypothesis, and was immediately embraced and added to the facts of neurology. This new decision, that dopamine caused muscles to relax, created a large group of corollaries, and a new (now proven wrong) theory about the cause and treatment of Parkinson's disease, one that would not die quickly.

### **1960's**

The nineteen sixties saw the creation of two new theories about Parkinson's disease. These new theories were based on two new drugs: one that could suppress acetylcholine and another drug that, once inside the brain, could convert into dopamine. Although both of these theories have turned out to be wrong, one can understand why researchers made the guesses that they did. Many doctors still subscribe to one or the other or both of these two outmoded theories.

### ***Levodopa, a variant of dopamine***

Some researchers noticed that brain dopamine, the molecule that had been labeled a muscle relaxant, was deficient in people with Parkinson's disease. This theory could not be tested in living patients, however, because dopamine, as noted above, was not able to pass through the blood-brain barrier. How then could one get dopamine into the brain to

test this theory? A solution to this problem came when a precursor molecule for dopamine, levodopa, or L-dopa, was shown to pass through the blood-brain barrier.<sup>1</sup> Once inside the brain, this precursor was rapidly converted into dopamine.

Levodopa experiments were then tried on human subjects with Parkinson's, with poor results. Although it appeared, based on chemical assay of rat brains, that levodopa did convert into dopamine in rodent brains, people with Parkinson's did not respond favorably to levodopa. Because people with Parkinson's did not respond to dopamine therapy, the theory that dopamine was responsible for Parkinson's disease stumbled.

### ***The opposites theory***

At this time it was not yet certain by any means that low dopamine levels were actually the cause of Parkinson's disease. This hypothesis was based, in part, on the theory of dopamine being a muscle relaxor, an opposite of acetylcholine. If there *were* two neurotransmitters instead of just one, if both acetylcholine *and* dopamine could affect motor function, the *two neurotransmitters must obviously have equal and opposite functions*. (Dear reader, don't even begin to worry about why they had to be opposites. It was an idea, the idea became published, and even today, now that more than 60 neurotransmitters have been found, there are still adherents to the "opposites" theory of neurotransmitters.)

An entire theory about Parkinson's disease was created to explain how a dopamine shortage must – via opposite theory – create an acetylcholine excess. This new theory required a new interpretation of all the symptoms of Parkinson's disease. According to this theory – one still held by elderly MDs – the symptoms of Parkinson's are caused by excess acetylcholine, acetylcholine no longer held in check by dopamine.

Because acetylcholine causes muscle tone, or muscle tension, the symptoms of Parkinson's were redescribed as being caused by excess muscle tone. Symptoms such as masked facial expression, which looks for all the world like sagging, lifeless muscles, were attributed now to excess muscle tension! In textbooks of this period, the feeble tremor of Parkinson's was attributed to excess motor strength. The heavy weariness of Parkinson's was described as a struggle against excess muscle tone. Although people with Parkinson's insisted that this was not the case, that their problem was difficulty in figuring out how to initiate movement, they were assured by the more modern doctors of this period that, in fact, their Parkinson's was due to excess motor function and too much muscle tone.<sup>2</sup>

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<sup>1</sup> Technically, DOPA should be all capital letters, as it is an acronym for di hydroxy phenyl alanine. In much of the older, technical writing, it is all caps. However, it is common now to see it as "dopa," or "L-dopa."

<sup>2</sup> Michael J Fox, a popular actor who has Parkinson's disease, wrote in his autobiography that it felt to him as if his Parkinson's disease was coming from his foot – which it was. His doctor assured him that his hunch was wrong. This modern problem of doctors denying a person's intuition about the source of a malady is particularly repugnant in light of the constant stream of errors and retractions coming from the medical community. Insult is added to a patient's injury or illness when the medical community, so rife with unproven hypothesis, squelches these insights from patients. It seems to me that if more doctors listened to their patients, they might find the cause of illness much more quickly. In the naturopathic school of medicine, it is said, "If you listen to your patient long enough and let him speak freely from his heart, he will eventually tell you, whether he knows it or not, exactly what the nature of the problem is, and what is needed to cure it, even though he may not consciously know the root of the problem nor its solution." Such listening requires not only extreme patience, but also humility.

### ***Questioning the cause of Parkinson's***

The older doctors were still uncertain. At this point no one had proved that dopamine deficiency was the cause of Parkinson's. Some still held to the turn of the century idea that Parkinson's was fear-based. Others were still interested in Charcot's 19<sup>th</sup> century idea that Parkinson's was an electrical disorder. (Both of these hunches, as it turns out, were partially correct.)

### **Proof: acetylcholine excess is the cause of Parkinson's disease**

In the early 1960's a belladonna-related chemical was shown to reduce Parkinson's tremor. This chemical was found to be an anti-acetylcholine molecule, also called an anticholinergic. Because this drug reduced tremor by reducing acetylcholine, it offered proof of the cause of Parkinson's disease: Parkinson's was caused by excess acetylcholine. Again, the proof was this: both tremor and also the high anxiety level of some PDers were reduced following the application of anticholinergic medication. Therefore, Parkinson's was caused by too much acetylcholine.

This school of thought had many adherents despite the curious observation that the other symptoms of Parkinson's disease (poor balance, slowness of movement, and rigidity) were all unaffected by anticholinergic medications. In fact, it did appear as if just the opposite was the case – anticholinergics *increased* slowness of movement. However, since the only drug that appeared to have any benefit whatsoever for PD patients was an anticholinergic, Parkinson's disease was, beyond a shadow of a doubt, caused by excess acetylcholine. This became one of the mid-twentieth century facts about Parkinson's.

### ***Proof and corollaries***

- 1) Medication that decreases acetylcholine (anticholinergics) reduces the cause of Parkinson's disease tremor and anxiety.
- 2) Anticholinergics, drugs that reduce muscle tension, are an effective treatment for Parkinson's disease.
- 3) People with Parkinson's disease have excess muscle tension. This muscle tension is the cause of their slowness of movement, rigidity, tremor, and balance problems. This tension is obviously caused by an excess of acetylcholine. (This was obvious because acetylcholine was at that time accepted as the neurotransmitter that caused muscle contraction.)

Please do not memorize the above. It has since been proved false.

### ***Gallons of levodopa – a new approach***

Meanwhile, experiments were ongoing with levodopa, trying to figure out why people who supposedly had acetylcholine excess didn't respond to levodopa. Because levodopa was a muscle relaxant, a supposed opposite to acetylcholine, it was assumed that Parkinson's could be managed by either using anticholinergics or by using dopamine. To this way of thinking, dopamine was, in effect, a form of anticholinergic.

Rat brains were able to convert levodopa into brain dopamine. People with Parkinson's, however, did not respond whatsoever to oral doses of levodopa. The failure of levodopa to help people with Parkinson's nearly rang a death knell to the theory that dopamine deficiency was a factor in Parkinson's disease.

## Appendix 5

Then, in 1967, a bold researcher, Dr. George Cotzias, tried using doses of L-dopa that were *thousands* of times higher than had been used previously. At these shocking, stunning levels of levodopa, an amazing result was obtained: people with Parkinson's appeared quickly to regain their lost motor function! Dr. Cotzias was hailed as a hero, and L-dopa was rapidly pronounced, by many, to be the cure for Parkinson's disease.

### **Proof: Parkinson's is caused by insufficient dopamine**

In the late 1960's, it was clear that people with Parkinson's were able to move more easily, albeit only somewhat normally, when their brains were flooded with levodopa. They also developed bizarre side effects from the drug. These side effects were attributed to various causes, and whole new theories sprung up. (One of the earliest theories, blood dopamine versus brain dopamine, still has adherents in the first decade of the twenty-first century, even though research has repeatedly shown that levodopa's adverse effects are due to brain levels of dopamine.) This finding led to some new (and since proven wrong) facts about the function of dopamine.

### ***Corollaries***

(Note that these corollaries are added onto the corollaries about acetylcholine excess. Unless absolutely necessary, outmoded medical theories are NOT abandoned. New theories are expected to build on existing theories.)

- 1) Dopamine allows people with Parkinson's disease to move, somehow neutralizing the tension from excess. Therefore, dopamine is *obviously* a relaxant.
- 2) Correct muscle movement requires a balanced blend of acetylcholine, a muscle tightener, and dopamine, a muscle relaxant.
- 3) Parkinson's disease is caused by an imbalance between acetylcholine and dopamine.
- 4) Since dopamine is a relaxant, it is undoubtedly released in large quantities during the night and especially during sleep. Adversely, during waking hours, dopamine levels decrease.

### ***The above is wrong***

Please do not memorize the above. It has all been proved false. High school kids today can tell you that the above is incorrect.<sup>1</sup> Your doctor, however, may not know that

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<sup>1</sup> I was sharing the material from this appendix at a weekend seminar. When I listed these above four points, I was interrupted by a high school student who chided me, "That's not the way dopamine works. We learned about dopamine in health class, in the unit on drug and alcohol abuse. It's a disinhibitor." This was in the year 1999. And yet the old theory of dopamine as relaxant was still being taught in medical schools up into the 1990's. To write an example here, I just grabbed off my shelf *Principles of Anatomy and Physiology*, G. Tortora, N. Anagnostakos, fifth edition, 1987, Harper & Row, NY, p 332. (Note: "DA" is biologist code for "dopamine.") This medical school text states that PD is caused by "severe reduction in DA in the basal ganglia... (and) diminished levels of DA cause unnecessary skeletal movement." There you are – not enough DA causes too much movement. Dopamine is a relaxant. In the same book, on p. 325 in the section on dopamine, the book states "DA leads to inhibition."

An example of how new data that conflicts with a cornerstone theory must be twisted to fit the existing theory is on this same page. It had been observed for nearly two decades that L-dopa caused excess movement in PDers, not increased relaxation. To make this conform to the existing "facts," this movement was explained away thusly on p. 325: "DA is involved in gross, subconscious movements of skeletal muscle." (Footnote continued on next page.)

this is no longer current. In retrospect, it is easy to see how the acetylcholine/dopamine imbalance conclusion came about. When I was in college back in the 1970's, busily engaged in growing germs in a petri dish, the above is what I was taught. I was taught it, by the way, not as hypothesis, but as stone cold fact.

### ***Problems with the dopamine deficiency theory***

PDers and their doctors soon noted that, while PDers could move more quickly after administration of levodopa, many of their other PD symptoms, such as tremor, cogwheeling of wrist and ankle joints, and balance problems very often did not respond to levodopa. Also, despite regular daily dosings of levodopa, PDers found that their condition continued to decline. This led the deeper thinkers of the medical world to refute the suggestion that levodopa was a solution and that Parkinson's was due to a dopamine deficiency. These doubters, as it turned out, were correct – but since the only treatment available that gave short-term relief was L-dopa, most doctors bought into the theory that dopamine deficiency is the cause of Parkinson's disease.

### ***False assumptions***

The observation that dopamine could impart faster movement to PDers turns out to be as irrelevant to the true underlying cause (original trigger) and correct treatment of Parkinson's disease as the observation that rum or whiskey imparts joy to a person with depression. No reasonable researcher would conclude, based on the temporary uplift from alcohol, that the underlying cause of clinical depression is alcohol deficiency in the brain. And yet a parallel to this supreme bit of illogic was applied to Parkinson's disease: since the bradykinesia (slow movement) of people with Parkinson's was assuaged for a few hours after partaking of levodopa, many doctors signed up to the school of thought that held dopamine deficiency to be the root cause of Parkinson's.

### ***An aside about levodopa research***

A famous L-dopa experiment took place in the late 1960's, two years after Cotzias gave massive doses of levodopa to PDers. This later experiment was so dramatic that it was made into a major motion picture (*Awakenings*, based somewhat loosely on the work described by Oliver Sacks in the book of the same name). This well-known experiment involved a group of eighty people with encephalitis caused by a viral plague in the 1920's, who had been in a condition of relative stupor for decades. Under the influence of massive amounts of L-dopa,<sup>1</sup> they were suddenly able to move, talk, and behave somewhat normally after having been more or less in suspended animation for three decades. The experiment developed unexpected side effects, however, as the patients soon began having hallucinations, violent spasming, and personality aberrations.

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(Footnote continued from previous page.) This was a way of keeping the old facts intact: DA was defined as a skeletal muscle *relaxor*, a movement *inhibitor* for conscious movement. Therefore, the excess movement that occurred as a result of L-dopa was due to DA having the *opposite* role for *subconscious* movement. There was NEVER any research that supported this idea of DA behaving oppositely in conscious and unconscious movement – the theory simply had to have these two contradictory parts so that the existing DA-as-muscle-relaxor theory could continue to stand in light of the facts that people exhibited excess movement when taking L-dopa.

<sup>1</sup> These dosages were as high as four *grams* (4000 mg) a day.

No matter how the L-dopa was titrated (carefully measured, with incremental increasing or decreasing of dosages), it appeared impossible to find the correct dose for these people, a dose level at which they could move and be awake and yet not suffer the monstrous side effects of the drug. Most of the patients died or had severe setbacks, some within a very short time, others within a few years of the experiments. Although there were a few exceptions where the L-dopa seemed somewhat beneficial if combined with other countering drugs, L-dopa, for purposes of this experiment, was ultimately decreed too dangerous and unpredictable for further use.

## 1970's

### *Levodopa use for Parkinson's grew in popularity*

Despite the uncertainty as to whether or not Parkinson's was actually caused by a dopamine deficiency, people with Parkinson's were finding L-dopa to be helpful in treating their slowness of movement, even though, within a few years on levodopa therapy, they too were beginning to show side effects similar to those of Sacks' patients. Curiously, people with Parkinson's who were using L-dopa had side effects that were less violent, less unpredictable, in the short term than people with other movement disorders who also experimented with this new drug. This observation, that people with Parkinson's had fewer side effects (at first) than other people with movement disorders, lent support to the faction that considered Parkinson's to be caused by a dopamine deficiency. But even people with Parkinson's fell victim to the unpredictable side effects of L-dopa within five years.

Within five years of Cotzias' experiments, it became apparent that L-dopa was not, in fact, a cure for Parkinson's. People with Parkinson's who had L-dopa therapy developed, within two to five years, traumatic side effects from the L-dopa. Increased doses of L-dopa appeared to accelerate the decline of the underlying PD symptoms and exacerbated the side effects.

L-dopa was no longer considered a cure. Worse, those doctors who had worked closely with Parkinson's patients during the years prior to L-dopa use and were familiar with the normal, undrugged pace of advancing Parkinson's noticed that the PD symptoms in people using levodopa therapy advanced more quickly than should have been expected based on the rate of Parkinson's decline in their undrugged patients. It appeared as if L-dopa accelerated the worsening of Parkinson's disease. Doubts were expressed as to whether or not dopamine deficiency was the cause of Parkinson's after all. Meanwhile, the acetylcholine excess theory was still holding firm in some quarters, and the dopamine theory was also strong. Many doctors did, and still do, continue to embrace both.

### **Proof: Parkinson's is caused by substantia nigra cell death**

Research conducted on brain autopsies of people with Parkinson's presented a puzzle. It did appear that an area in the dark, almost blackish, center of the brain, the substantia nigra, was different in PDers. The cellular change was curious. Some of the cells in this blackish area were no longer black, but had reverted back to a more neutral color. In some, though not all, of the brains there was even evidence of cell death. Because few people suspected at this time that levodopa itself could cause brain cell

death, it was assumed that any and all changes seen in the substantia nigra of PDers, including cell death, must be due to Parkinson's.

This did not prove that changes in the substantia nigra caused Parkinson's, but it did suggest an association. Some people held that Parkinson's disease caused the change in brain cells, others proposed that the change in brain cells caused Parkinson's. Researchers discovered that this darkly pigmented area was rich in dopamine. Jumping to an unfounded conclusion, they decided (erroneously, it turns out), that all brain dopamine was produced in the substantia nigra. This suggested a connection between the facts that 1) PDers had changes in their substantia nigra and 2) they responded to levodopa.<sup>1</sup>

Still, even with all this information, the fact remained: levodopa only addressed a few of the many symptoms of Parkinson's disease. It had not been conclusively proven that dopamine deficiency, and certainly not cell death in the substantia nigra, were the underlying cause of Parkinson's.

### 1980's

By the 1980's dozens of neurotransmitters had been discovered. Dopamine was no longer considered to be the opposite of acetylcholine. Dopamine had been reassigned: it was now the opposite for serotonin, a frontal lobe neurotransmitter. The "opposites" theory was dying; too many neurotransmitters had been found and their functions appeared to overlap more often than oppose. However, some turn of the millenium pharmaceutical texts still refer to dopamine as the opposite of serotonin.

### *Frozen Addicts*

In 1982 a new piece of information appeared which was vigorously massaged to "prove" the cell death theory of Parkinson's. A group of drug addicts (made famous in the book *The Frozen Addicts* by Dr. Joseph Langston) overdosed on MPTP, a designer drug that is supposed to resemble heroin, after which they were unable to move. Their paralysis suggested, somewhat, the immobility of Parkinson's. These addicts were able to move again after they were administered high doses of L-dopa.

Using lab animals, it was shown that this drug (MPTP) was lethal to certain brain cells, substantia nigra cells in particular. Dr. Langston jumped to the conclusion that, because these brain-damaged addicts could not initiate movement, and their movement

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<sup>1</sup> It was discovered much, much later, in the late 1990's, that a decrease in the darkened areas of the substantia nigra is a normal consequence of aging. This normal decrease occurs in the back part of the substantia nigra, while in Parkinson's, the decrease is usually in the front part.

(I should reference this study, of course, and all of the studies that I quote. But I have been very bad at organizing and saving all of the thousands of references that I have read. But then, I never intended to write a book, so why should I have saved references to everything I was reading about? At some point, when I realized that my writings on Parkinson's medications should be assembled into book form, I had to decide between putting in a few extra years to find all the footnotes, or else getting this book out as soon as possible to help the greatest number of people. Possibly future editions will pay more attention to scholarly attribution.)

Another study (one was done in Germany, another similar one was done by either the Mayo or Johns-Hopkins clinic, in the late 1990's – forgive me) found, based on post-mortem brain exams, that a *significant percentage of people who had been diagnosed with Parkinson's disease did not have any abnormal decrease in the dark cells of the substantia nigra*. I have never seen any follow up on either of these studies, a common fate for research that does not conform to expectations. I seem to remember that a conclusion to the study was that doctors had evidently been incorrect in their diagnoses.

initiation was restored with levodopa, he had proved the cause of Parkinson's disease: Parkinson's was caused by brain cell death, and more than likely, the source of the cell death was some as yet unknown external agent.

In retrospect, Dr. Langston probably should have said that the drug-induced brain damage caused Parkinson's-like symptoms. Instead, he boldly declared that he had confirmed the cause of idiopathic Parkinson's disease: Parkinson's disease was caused by the death of substantia nigra cells. This hypothesis and his extra hypothesis, that damage to the dopamine-producing area was probably caused by environmental agents was touted *regardless of the facts that the symptoms of the addicts were significantly different in many ways from the symptoms of Parkinson's disease, and the brain cell changes were also significantly different.*

Langston's questionable logic was hailed by most neurologists.<sup>1</sup> The previous theory about acetylcholine/dopamine imbalance was integrated into a new theory that worked with the substantia nigra cell death/environmental toxin theory.

### 1990's

By the 1990's, more than 50 neurotransmitters had been identified. The opposites theory was long dead (although still used by some neurologists in their explanation of Parkinson's disease, and the manufacturers of anticholinergic medications still refer to their drugs as adjusting the dopamine/acetylcholine imbalance). The hormone vs. neurotransmitter debate was not only dead, it was long forgotten; neurotransmitters were obviously made in nearly every cell of the body and traveled freely from stem to stern. Even though the blood-brain barrier prevented some neurotransmitters from moving between the extracerebellar (body) areas and the brain, neurotransmitters manufactured anywhere in the body were clearly influencing neurotransmitters in all other body parts.

### *Proof positive*

These 1980's hypotheses about dopamine were so widely embraced that the dopamine – substantia nigra cell death – Parkinson's connection was accepted as unassailable fact by the 1990's. During this decade various official numbers were even assigned describing just how much substantia nigra cell death had to occur before Parkinson's appeared: PD symptoms appeared when "60% of the nigral nerve cells disappeared."<sup>2</sup>

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<sup>1</sup> This theory has been a goldmine for researchers. Millions of dollars in grant money are currently being poured into research on how to stop this inexplicable cell death from mystery environmental toxins, even though other research has proved that the substantia nigra cells in idiopathic Parkinson's are not, in fact, dead.

At a lecture by a prominent Parkinson's researcher, he bragged about the twelve million dollars that his company had received to study drugs that would protect cells against "Parkinson-causing cell death." A member of the audience raised his hand and queried, "Why are you researching how to prevent cell death when the new research indicates that the cells are merely dormant and not dead?" The researcher didn't miss a beat, and countered, "It doesn't matter whether the cells are alive or dead, there is still not enough dopamine so we want to stop these cells from dying." Was he listening to himself? He didn't make much sense, but I suppose twelve million is hard to argue with.

<sup>2</sup>A. Lieberman, MD, Curing Parkinson's Disease in our Lifetime, *Parkinson's Report*, National Parkinson's Foundation, Fall 2000, p. 10. This nice, round, theoretical number has no basis. This number was determined by guessing backwards. (Footnote continued on next page.)

Also in the 1990's, research proved that L-dopa accelerates the worsening of Parkinson's disease. Dopamine agonists were shown to also cause acceleration of Parkinson's, but not to the same extent as L-dopa.

Researchers in the field of Parkinson's rely on rodent "models" of Parkinson's disease for their experiments. Even though it was suspected (and has now been proven) that idiopathic Parkinson's disease is not caused by toxins, rodents are purposely brain damaged via toxins, and then studied as if they represent a valid model for Parkinson's. While I am on this subject, please be wary: whenever you read about a new breakthrough for Parkinson's disease, read carefully in the fine print. If the research was done on a "model" of Parkinson's disease, or done on animals with "parkinsonism," the results have little or nothing to do with idiopathic Parkinson's disease, and the researchers are well aware of the fact. However, since blinding amounts of research money is available for Parkinson's, and there is no way to actually create idiopathic Parkinson's disease in a lab, these "models" of Parkinson's are used in research.

Again, drug- and toxin-induced cell death parkinsonism has almost nothing in common with cell-dormant Parkinson's disease. Studying the former in hopes of learning about the latter is pointless, especially since the direction of research is usually oriented towards finding a way to prevent cell death – a cell death that does not occur in Parkinson's disease. Your tax dollars at work...

### How science grows

Right from the start there were inconsistencies with the Frozen Addict = Parkinson's disease conclusion. There were notable physical differences between people with Parkinson's disease and those who, like the frozen addicts, had drug-induced or toxin-induced movement inhibition.

For example, the addicts had developed a rapid onset, complete body paralysis, and PDers usually develop rigidity very slowly. The addicts had immobility due to inability to initiate movement. PDers, in addition to difficulty in initiating movement, have a host of symptoms that are not found in "frozen addicts," symptoms such as a

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(Footnote continued from previous page.) At the time this number was proposed, there were no methods of measuring brain change except for autopsy. This beautifully exact number, 60%, was pure guesswork based on autopsies of PDers. The number was attained by extrapolating the amount of cell change visible after death and comparing it to what it might have been at the time of diagnosis. The now-known fact that *the drugs that had been given to the PDers who were autopsied actually cause cell death* was not considered at the time these numbers were created. Very possibly, the brains that were used to create this 60% statistic were actually damaged by the drugs, more than by the idiopathic PD.

Moving beyond the numbers game, it is fun to read further in *this same paragraph* by A. Lieberman that, in Parkinson's disease, "although dopamine is depleted, *the cells in the striatum are preserved*. This is unlike the PD-like disorders (drug- and toxin-induced parkinsonisms) where, in the striatum, the dopamine content is decreased and *the cells are lost*" (emphasis added). In case that got by you too quickly, what the MD director of the National Parkinson's Foundation states, all in one paragraph, is that, 1) by the time PD appears, "60% of the cells have disappeared" (or "are lost," the old established fact), and 2) the exact opposite position (the new evidence), namely, that in Parkinson's disease, the cells are preserved! The cells are "disappeared" and "preserved" both, all in one paragraph! Hats off!

This just in! In a new book that just crossed my desk, I read that Parkinson's disease "results when 80 to 90 percent of the dopamine neurons are lost." This tidbit is from the 2001 edition of *A Primer of Drug Action*, R. Julien, MD, PhD. Henry Holt and Company, p. 358. Don't memorize these numbers – they will doubtless be changing again soon.

characteristic rigidity in specific joints that causes a cogwheeling motion in the wrists and ankles, and they have inflexibility of specific muscles of the torso, unresponsiveness to brain command in the anteriolateral muscles of the legs and neck muscles, use of certain facial muscles but collapse of others, degeneration of the bicep, atrophy in the muscle alongside the second metacarpal, and dozens of other PD-specific symptoms. Most significantly, Parkinson's disease usually develops on one side of the body and only after some time does it become two-sided. Even after it spreads to the second side there is usually a distinct difference between the sides.<sup>1</sup>

Also, the addicts did not have the same type of tremoring along the Large Intestine and Stomach channel lines, balance problems, personality profile, circulatory problems, constipation, hardening of anteriolateral skeletal muscle, or seborrheal skin problems that were seen in PD, and other details that should have suggested a difference between drug- and/or toxin-induced parkinsonism (as it is now called) and idiopathic Parkinson's disease.<sup>2</sup>

However, the L-dopa as cure theory had already been embraced even though L-dopa was suspected to increase the advancement of Parkinson's symptoms and only some, not all PD symptoms responded to L-dopa. The brain cell death theory was added on. As there was no reason to discard the excess acetylcholine theory, that theory was also maintained.

### *The way of all science*

Scientists like to build on previous information. The PD-is-caused-by-dopamine-cell-death theory, together with the dopamine-as-relaxant theory were established, by the mid 1980's, as the cornerstone theory upon which all future PD/dopamine research would have to stand.

Once a theory becomes a cornerstone, it requires a paradigm shift – ideological dynamite – to change the theory. The problem with changing a cornerstone theory is that all of the theories that have been built on top of the cornerstone will topple. The political

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<sup>1</sup> This may not seem significant to you, but an all-over disease can be best attributed to a systemic failure in the system or ingested toxins, whereas an asymmetrical disorder can usually be traced to an injury, insult, or localized illness on only one part of the body, such as is seen in stroke or polio. The one-sidedness of Parkinson's onset is actually a major clue as to the source of the physiological changes that eventually trigger the PD symptoms.

<sup>2</sup> Dr. Langston's work was done back in 1982. Now, in 2003, the idea that drugs, including legal, pharmaceutical drugs, do cause parkinsonism is old news. The latest edition of *Parkinson's Disease, Questions and Answers*, Merit Publishing, with a forward by the medical director for the National Parkinson's Foundation, has an entire section on "Which medications cause parkinsonism?" In that section the author notes that "Many pharmacologic agents can produce features of parkinsonism, including tremor, bradykinesia, rigidity, speech disturbances, and akathisia. These include dopamine-blockers such as the neuroleptics" (My note – these drugs are often prescribed to PDers who are having dyskinesia rather than telling the PDers to reduce their dyskinesia-inducing drugs.) "and antiemetics, as well as dopamine depleters, the gastrointestinal motility drug metochlopramide, lithium, alpha-methyl-dopa, and some of the tricyclic antidepressants." The author goes on to list other drugs that can cause parkinsonism, and ends with stating that "anyone who has recently used these medications should be observed for at least six months off the medication before a diagnosis of Parkinson's disease is made."

Despite these published warnings, I frequently meet patients who were taking antidepressants from the above group who developed signs of parkinsonism and whose MDs then started them on PD drugs without a moment's hesitation.

force behind a cornerstone theory is strong: trying to disprove these theories can destroy a scientist's career.<sup>1</sup> Evidence that contradicts the cornerstone is assumed to be faulty. In the case of Parkinson's disease, those patients whose responses to L-dopa contradicted the new theories were accused of having the wrong response!

***An example: patients are wrong if their response doesn't match the theory***

In the first decades of L-dopa use, many, if not most, PDers complained to their doctors that L-dopa was causing them, among other adverse effects, a severe type of insomnia. As an example of the inertia of science, and what happens when the cornerstone is contradicted, here is what happened to these complainers: *they were told that they were wrong.*

Here's why they had to be wrong:

1) Parkinson's is a disease of excess tension (ACh excess theory).

2) L-dopa cures Parkinson's.

Therefore:

3) Dopamine is a relaxant.

4) Humans are more relaxed when sleeping.

Therefore:

5) Dopamine is at highest levels at night and when sleeping.

6) L-dopa is therefore a sleeping aid.

7) Patients who take L-dopa should not attribute their insomnia to the drug, because the drug helps them sleep.

Please do not memorize the above. The above has since been proven wrong. Native dopamine levels naturally drop to very low levels during sleep. Also, as it turns out, L-dopa is not a muscle relaxant, it is an anxiety suppressor and motor *stimulant*.

The above seven-step proof was so logical that a drug company-sponsored study was conducted to disprove the contention made by PDers that their L-dopa medication was causing severe insomnia. Experiments were run comparing the sleep patterns of PDers who took the L-dopa at night or late in the evening compared to those who did not. The results of the study *proved that the complaining patients were correct: taking the medication late in the evening or at night was associated with increased insomnia.*

Despite the finding that L-dopa was, in fact, linked to insomnia, the official (if illogical) conclusion of the study was that (and I paraphrase), even though the medication *appeared* to be a major cause of insomnia in users of L-dopa, the *obvious* (their words, my italics) benefits of having consistent levels of L-dopa in the body throughout the day and night should override the insomnia concern.<sup>2</sup> Also, it was a fact (see step 5 in the

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<sup>1</sup> As an example of the dangers inherent in challenging a current scientific paradigm, Galileo Galilei, who insisted that the movement of heavenly bodies was more orderly if the sun, not the earth, was the center of the planetary orbits, lived out his days under house arrest. His fellow astronomers, who, for the most part, snapped up his writings and recognized him as a genius, were afraid to publicly support him.

<sup>2</sup> A citation for this article is in order, but I don't have it. The abstract on this article was one of the ones that came up in the 100 abstracts mentioned later in the next appendix. Go to med base and do a search for dopamine/sleep. I did the search in August of 1998.

above proof) that dopamine levels should be higher at night. Therefore (concluded the study), the insomnia problem, though seemingly caused by the L-dopa, was probably being generated by some unknown.

This trend, in which patients who have problems with their drugs are told that they are wrong, and that the drugs are not causing problems, is increasingly the norm. In medical schools today, would-be doctors are often taught that patients' adverse responses to medications are usually psychosomatic, and that patients should not even be warned of the side effects for fear that they will develop them. But the above study was even more alarming: the study indicated that insomnia was being caused by the drugs, and yet the stated conclusion of the study was that the drugs should still be used during the night. The implication was that the drugs should be used even if they caused harm.

Other patient complaints about the drugs were usually met with the same sort of nonchalant shrug on the part of doctors. The accepted medical position was, by the late 1990's, that Parkinson's disease was caused by dopamine loss due to substantia nigra cell death, and people with Parkinson's should take whatever medications they needed to increase brain levels of dopamine.

## 2000

By the year 2000, over sixty neurotransmitters had been identified. They appear to influence nearly all cellular functions. The complexity of neurotransmitter interactions, the effect of neurotransmitters on mental activity and the effect of volitional mental activity on neurotransmitters has begun to make the old idea of brain-as-switchboard look positively quaint. Increasingly, some molecular biologists now suspect that thought initiates release or creation of neurotransmitters, rather than the reverse. However, some neurologists, especially those who went to school prior to 1980, still consider that there are only a few crucial neurotransmitters, and that Parkinson's disease is caused by dopamine deficiency and possibly excess acetylcholine.

As for Parkinson's research, the largely ignored research at the turn of the millennium proved that a substantial difference existed between people with idiopathic Parkinson's and those with drug- or toxin-induced parkinsonism. In those with idiopathic Parkinson's, the cells of the striatum are not dead.

This should-be shocking news has been, for the most part, ignored by most MDs and PD researchers. The problem with this new finding is that it suggests that there might be some obscure, unknown reason that the cells are not making dopamine. The cell dormancy seen in PD might mean that what is needed for PDers is not necessarily dopamine, but a way to make these cells start producing dopamine again. Since western researchers don't know what causes cells to differentiate and create their various cell components, they have no way to use this new information about cell change. Since there is no way to pharmaceutically benefit from these new findings, the new research is largely ignored in the applied medical (clinical) realm.

Further research has shown that, in idiopathic Parkinson's, the dopamine receptor cells do not necessarily accept dopamine even when it is foisted onto the brain via dopamine-enhancing drugs. In other words, it begins to appear as if the brain of idiopathic PDers is *resisting* dopamine, not suffering from a dopamine shortage.

This conclusion, that PDer brains are trying to resist dopamine, is not helpful to MDs because western medicine has no method by which to reverse this shunning of

dopamine. Therefore, because the only tools available to ameliorate a few of the symptoms of PD are drugs that force dopamine onto a brain that is trying to resist dopamine, those tools are the ones that are used. Rather like the man whose only tool is a hammer and for whom all problems therefore look like nails, MDs have no tools other than dopamine-enhancing drugs, and so all PD problems continue to look like dopamine deficiency to this group of doctors.

### ***Acetylcholine, again***

Recognizing that PDers have difficulty initiating movement, combined with the fact that acetylcholine is a muscle stimulant, some bold young researchers and doctors have started using drugs that enhance acetylcholine in the treatment of Parkinson's. While these drugs exacerbate tremor, they can sometimes help, briefly, with the Parkinson's slowness of movement. This is a 180° reversal of the treatments offered from 1960 to the present. I have even heard from patients simultaneously being prescribe both anticholinergics and cholinergics! This type of error is not shocking; I have learned that many doctors prescribe pills based simply on whether or not a drug is on the list of "antiparkinson's medications," while having no idea about the mechanism by which the drugs perform their job.

### ***Dopamine and addiction***

In 2000, dopamine was recognized as the chemical of addiction, the neurotransmitter of pleasure. It has now been proven that the various addictive drugs and substances, including cocaine, opiates, methamphetamine, alcohol, and cigarettes are all addictive because of their ability to elevate, however briefly, brain dopamine levels.

### ***Dopamine's many hats***

Dopamine is recognized as a powerful mind and motor stimulant. Dopamine decreases pain awareness. Excess dopamine combined with insufficient frontal lobe activity causes schizophrenia. Excess dopamine alternating with insufficient dopamine is the neurotransmitter imbalance that causes bipolar (manic-depressive) behavior. Dopamine helps regulate body temperature. Dopamine levels affect the immune system. Dopamine is used in sedating stress from social interactions. Dopamine levels are highest during waking hours, and decrease drastically during sleep. Dopamine is used not to stimulate motor function nerves, but to bridge the gap between thought and motor function.

The brain is exquisitely calibrated to maintain dopamine at exactly correct levels: too little causes severe depression and too much causes illogical ecstasy. It is impossible to administer dopamine-enhancing drugs in a manner that can replicate the sublime balancing act performed by the brain in regulating dopamine. Any application of a dopamine-enhancing drug that attains the desired effect must necessarily broach the line above which drug addiction and brain cell damage occurs.

As for the relationship between thought and neurotransmitter release, it has been shown that dopamine is the most expectation-dependent of the neurotransmitters: if a person imagines that he will feel better, he does in fact feel better. This improvement in his mood and energy is directly related to an increase in dopamine that occurs in response

to the expectation of improvement. Conversely, a conviction that one is going to feel worse is accompanied by a decrease in dopamine.

The placebo effect, a benefit that can occur in treatment of some illnesses and not in others, appears to primarily play a part in those illnesses that have a dopamine-related component. Dopamine imbalance plays a part in a variety of illnesses, from asthma to insomnia, from schizophrenia to Parkinson's disease.

## *Summary*

The theories about Parkinson's disease changed frequently from 1950 to 2000. Doctors are currently practicing medicine who subscribe to the excess acetylcholine theory, or the acetylcholine/dopamine imbalance theory, the dopamine deficiency theory, the substantia nigra cell death theory, or most recently, the dopamine resistance theory. The theory to which a doctor subscribes very possibly is determined by the year he attended college.

### *Drug prescriptions*

The drug prescribing patterns of a doctor may very well be determined by the prescribing that was popular during the doctor's intern years. Some doctors still use anticholinergic (anti-acetylcholine) medications. Some young doctors are using the opposite: acetylcholine-enhancing medication. Older doctors usually tout L-dopa. Younger doctors often shun L-dopa or tell patients that it is a drug of last resort, while exhorting the virtues of the newer dopamine enhancers.

Most doctors, believe it or not, do not realize that the various antiparkinson's drugs have different effects. Few doctors in my experience have understood that anticholinergics should only be used in patients whose dominant problem is tremor or anxiety, patients who do not have serious motor initiation difficulty. Other doctors do not know that L-dopa, a drug that causes increase in motor initiation and an increase in tremor should *not* be used for patients whose main complaint is tremor.

In my limited experience, I have seen that most doctors, even Parkinson's specialists, simply throw at their patients whichever antiparkinson's drugs they are most accustomed to using, despite the tremendous variety in PD symptoms presented by their patients. If one drug doesn't seem to work, or becomes ineffective, the useless drug is almost never removed from the medication roster, but is retained, while more drugs are piled on top.

What a neurologist learned about dopamine in medical school may or may not be the view of dopamine in your Sunday newspaper column on Ask The Doctor. The view of dopamine that your spouse or loved ones might hear on TV talk shows about dopamine can vary dramatically, depending on which year's medical dictionary is being used as a reference. Your fourteen-year old niece probably knows that dopamine is the neurotransmitter of addiction. If your health care provider went to school some time between 1960 and 1995, he probably does not know this. Your neighborhood biochemist may know about the exciting new world of neurotransmitters. Your neurologist may not know about any of the exciting new findings in the field of neurotransmitters, and may instead subscribe to some or all of the outdated dopamine/Parkinson's theories included in this appendix.

The various theories explained in this appendix were the cornerstone facts for Parkinson's disease during the second half of the twentieth century. They were the paradigms of Parkinson's, and most neurologists that are currently practicing medicine will not let go of them without a fight. These various outdated theories are still, for most neurologists, the alpha and the omega of Parkinson's disease.

This appendix was written to hopefully make the point that medical facts are inconstant, and that there is no such thing as a standard of medical knowledge. For those who are struggling with family members who demand allegiance to the all-knowing doctor, this appendix may not help, but on the long-shot chance that it might, I offer it to you. I also enjoyed writing it because it was a History of Science class, a college course that traced the creation and destruction of scientific myths, from the days of Plato to the Einsteinian twentieth century, that first opened my eyes to the realization that the "facts" that I was memorizing in my biology classes were simply the current theories, and no more related to Truth than the now laughably false dictums of Aristotle. This class was the catalyst that turned me away from my pedantic study of biology "facts," fanning my interest in both history and modern physics, and giving me the strength to pursue my medical research even when it flew in the face of the established theories. As an example of my own run-in with hard-to-change establishment thinking, I have included in the next appendix the true tale of my first confrontation with dopamine fallacies.

