

## Appendix 11

# GUESS WORK ABOUT BUILD UPS:

## HOW RESEARCH STUMBLES ALONG

So that you can follow along with our thinking, and maybe do some of your own that will help you see your way clearly through all this, let me share what was going through our minds as we pondered the Build Up.

What exactly goes on with the Build Up? Just what mechanism(s?) does the brain use to initiate short-term (single dose-related) Offs when dopamine levels rise? Does it shut down vesicle doors? Does it inhibit transport molecules?

It doesn't really matter, but we remain curious. I think curiosity is an inherent human condition. So here is our thinking about the build up.

We figured there were two likely possibilities: an enzymatic response that affected dopamine metabolism, transport, or uptake, or else a short-term receptor shutdown. In lay terms, to use a deliveryman analogy, either the deliveryman wasn't making the delivery, or else the deliveryman was there with the goods but no one was answering the door. You don't really have to read the following Fun Ideas, but if you want to see the kinds of thinking we research types tumble around in our heads, here it is. If you'd rather walk the dog or wash the car, go right ahead.

### *Fun Idea #1*

The first idea, in which the deliveryman is not able to deliver the package, requires a more complex mechanism than the second. To explain why the Build Up occurred in a 24-hour cycle, it was first necessary to propose a dopamine half-life in the brain of, let's say, twelve hours. This "educated guess" is based on the observation that some patterns repeated every twenty-four hours. In this case, the first dose would work fine, but as overall dopamine levels increased during the day, the dopamine-resistance mechanisms (decreasing the transport and other enzymes) or an emergency rigidity mechanism (dopamine override) would be initiated. But in which part of the brain would this be registered? The limbic area might be too slow to change; it might have to be a mid brain, motor area, or frontal lobe response. To explain what we saw, it would need to be a graduated response: the quantity of shut down mechanisms was tied to the quantity of the (relatively) excess dopamine. That would be the only way to explain that Build Ups could be either mild or severe, and that each subsequent dose might work slightly less well. The brain response would have to be graduated and not a threshold event,

Of course, maybe the symptom of freezing from overmedication could be caused by a threshold sort of action, an upper threshold above which movement is not allowed, just as there is a lower threshold below which movement cannot occur.<sup>1</sup> The upper

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<sup>1</sup> The upper threshold idea is not without a corollary in everyday (non-drug related) life. We all recognize that with deep concentration (an act which increases energy flow through the middle of the brain as opposed to the sides, and which therefore might increase dopamine levels), the body does grow still and breathing becomes slow. Unlike the fretful monkey who is in constant motion and breathing fast, a person

threshold idea might apply in this case, as the build up of dopamine might be increasingly poking its nose above the upper threshold. Even though the brain might be trying to dismantle the incoming dopamine, each new dose would shove the total that much higher above the threshold, and the Offs from excess would increase in length. By the next morning, the dopamine levels would be low enough so that the first dose of the day wouldn't violate the upper threshold.

This thinking would require the dopamine break-up mechanism to be fairly quick, completing its job within 24 hours at the most. Considering that doses were very often taken in the evening, and yet a person was back down to the daily starting place again by morning, we might need to propose a 12-hour break-up mechanism.

The above is just musing, to show you the kind of thinking we were doing.

### ***Fun Idea #2***

The second idea, in which no one is home to receive the package, is based on the finding that the dopamine receptors in the brain do have a shut-off mechanism, as demonstrated in nicotine research: once a dopamine receptor has been used by a nicotine molecule, it can't be used again for a period of twelve hours. A short-term (twelve-hour) shut off would explain why the end-of-the-day drugs don't work as well as the beginning-of-the-day drugs.

Again, this is just a guess. We don't know exactly what is happening. These are just some thoughts that we've had. Let's leave something for the biochemists to detail out. But it's important for us to recognize that, whatever mechanism is being used, the brain does *not* go back down to zero after each dose wears off, but is in fact still responding, somehow, to the dopamine that has already come in that day. Either the receptors are shut down, a threshold has been crossed, or some unknown mechanism is

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intent on a specific task can be very still for a long time. An extreme example of this is the whole-body rigidity that occurs during deep meditation when the breathing stops or very nearly stops. This rigidity is not at all like that of a soldier who is trying to stand still during roll call. The soldier is making an effort. The yogi, sage, or saint is utterly relaxed. His is a rigidity that occurs when the mind literally withdraws from the sensations of the body.

As the sensory nerves are turned off and the mind is completely centered (literally centered, in many cases, on focal points (chakras) in the medulla, midbrain, or forehead), the body becomes as if frozen. It is a rare sensation. It is not so much that the body cannot initiate movement, but that the body has no desire whatsoever to initiate movement.

It does feel, during such a time, as if the brain chemistry has been altered. The concomitant state of deep peace or bliss that accompanies such stillness is a noble relative of the spritz of bliss that is experienced by a drug user. The fleeting, false joy of the drug user is evidently seen as dangerous by the brain: it triggers an addiction response. The peace that wells up within a person of prayer or meditation appears to be a response to patient brain restructuring. This restructuring may make a permanent increase in dopamine levels. This lasting redirection of the brain towards peace, wisdom, and ever-new bliss by increasing divine attunement in the soul-radio might be attained via the vibrating molecule of dopamine. Unlike the deluge of dopamine that accompanies drug use, the dopamine increase in a person of prayer is gradual and exact. Obviously, in the latter case, the proposed Safety Limit is never violated, and may, in fact, through training, be raised to allow for beneficial, ever-higher dopamine levels.

The possible relationship between dopamine and spirit is fascinating and, as you have guessed already, beyond the scope of this book. But even the possibility of a relationship between dopamine and divine joy helps to explain both the allure of dopamine and the brain's cut-and-slash response to any dopamine excess. While the man of spirit may want to "die daily," into the breathless stillness of God communion, the animal limbic system wants no part of death!

responding to the accumulation of dopamine. This is why the later pills of the day can be so often unreliable or their side effects so violent.

Just by looking at the Build Up, we can't really tell which mechanism, if either, is more likely. But when we consider the evidence of the Daily Deficit, we lean more towards the idea that dopamine is accumulating over the course of the day. However, given the proven (for what that's worth) 12-hour reset button that has been seen in DA receptors in the nicotine experiment, and given the complexity of the brain, it's possible that both effects are occurring, if not three or even fifteen systems that we haven't even imagined. There may be both a build-up of dopamine over the course of the day, triggering reduction of dopamine-processing enzymes and closing of vesicles, and *also* a temporary shut down of receptors, plus dozens of other subtle brain-balancing acts. But what is important for us is this: neither one of these ideas has any relationship to the purported 1 to 3 hour half-life of the various medications in the bloodstream that are preached by the drug companies.

Of course, we have no idea what the actual mechanism is. Possibly the mechanism has to do with shutting the doors to all dopamine vesicles so that no more dopamine can be released. Or maybe transport enzymes are involved. We have no idea of the process, but we named this Off process that was occurring at highest dopamine altitudes the "Shut Off switch."

Our mental picture of the shut off switch is a circuit breaker that can be flipped in response to an upper threshold breach. This upper threshold is far above the Safety Limit. The Safety Limit merely registers that dopamine is present in any quantity above that which is needed. A violation of the Safety Limit begins an addiction process to moderate future dopamine levels. The addiction process occurs when the Safety Limit merely notices an unhealthy level of dopamine.

The Shut-Off switch is an abrupt, immediate, curtain-dropping shut down that freezes the body on the spot while it rallies all of its dopamine-reducing forces. Once the demolition crew has broken up and carted away enough dopamine to bring the levels back down to a merely addictive level, rather than a near-death-inducing one, the circuit breaker flips on again, and the On might resume. Sometimes the second On of a Roller Coaster might be followed by a loud Crash, but often, after enduring a Roller Coaster, the next pill of the day might work more predictably. This might be because the demolition crew overplayed its part and brought dopamine levels so drastically low that the next pill would play out its part completely within the On zone, rather than going up into the excessive, dyskinesia range.

What are your ideas on the subject? Isn't science fun?

