

Bromocriptine: An Old Drug with New Uses

by
Lyle McDonald

This book is not intended for the treatment or prevention of disease, nor as a substitute for medical treatment, nor as an alternative to medical advice. It is a review of scientific evidence presented for information purposes only. Recommendations outlined herein should not be adopted without a full review of the scientific references provided and consultation with a physician. Use of the guidelines in this booklet is at the sole choice and risk of the reader.

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ISBN: 0-9671456-1-9

FIRST EDITION
FIRST PRINTING

Acknowledgements

Generally, I want to thank all of the people who seem to enjoy what I have to say, who read my articles, and who tell me that my advice has brought them results. I wouldn't keep doing this if they didn't, and I wouldn't be where I am today without these folks' support.

Specifically I want to thank all of my test readers and editors: Seth Breidbart, Nina Bargiel, and Lester Long. Their comments, corrections, and endless feedback prevented this from being another hard-to-read, typo-laden effort.

I want to give a special thanks to Shelly Hominuk, webmistress of <http://www.QFAC.com>. First and foremost I want to thank her for her help in bringing this book into existence, first in its digital form. She's a techmistress in addition to being a stone hottie. Also, I want to thank her for putting up with my shit for so many years.

I also want to give a special thank you to Laura Moore, sex guru, for her feedback on the small section about bromocriptine and sexual function. And for also being a stone hottie who has put up with my shit for many years.

I want to give extra special thanks to my partner in crime: bench press stud and endocrinology nerdette, Elzi Volk. On top of her editing efforts on this and my last project, she has been a sounding board and constant source of questions, criticism, and information over the years. She's put up with more shit from me over the years than I can ever thank her for. I am truly indebted to her.

It should go without saying but I'll say it anyhow, Dan Duchaine (R.I.P.) deserves a level of thanks I can never give him. He quite literally made me whatever I am today. We miss you, Dan.

Finally, I want to give a super-duper extra-special thanks to John M. Williams. Without his constant efforts, this project would never have become what it is.

Foreword

I'm assuming that most of you who have picked up this booklet know me through my articles on the internet, the occasional print magazine work I've done, or through my first book on ketogenic diets. If not, you have no clue to who I am so you might as well just turn to Chapter 1. If you do know me, you probably know that I usually don't talk much about drugs. Contrary to what some have occasionally suggested, this has nothing to do with any moral stance on my part.

Overall, I consider myself a libertarian when it comes to the use of drugs. As long as the choice is made based on knowledge, and no one but the individual making that choice is affected, what people do to themselves is their own business as far as I'm concerned. So if it's not some silly moral anti-drug stance, why don't I talk about drugs very much? There are a few reasons.

The main reason is that drug solutions for body recomposition (a fancy word that means more muscle, less fat, or both) have never been my real interest or fort . I've always been interested in pursuing better approaches to training or nutrition in hopes that solutions would be forthcoming. Additionally, there were always people out there who had forgotten more about drugs than I could ever know. I figured I'd leave the drug stuff to them, and focus on my own area of expertise. Why try to compete with guys who did nothing but research drug solutions when it wasn't my major interest?

At the same time, I've always sort of kept myself aware of some of the drugs that were floating around and looked into them from time to time. Sometimes finding the way that certain drugs work can often lead to a more 'natural' (a loaded word if ever there were one) way of accomplishing the same thing. That is, figure out the mechanism behind something like clenbuterol, and you can figure out ways to mimic it to at least some degree with other compounds such as ephedrine.

As I've lost some of my youthful idealism, become more of a realist, and learned more about human physiology, I've come to the rather depressing realization that there are limits to what can be achieved 'naturally'. Our bodies are simply too smart and too adaptable, which explains why most of what we do (or can do) only works to a limited degree.

As I'll detail in an upcoming book project (my magnum opus as it were), our bodies are smarter than we are which is why most non-drug solutions are only minimally effective. In a very real sense, in terms of what we typically want to

accomplish, our bodies hate us. Ten million plus years of evolution have made it so: our bodies want to keep us alive and will do just about anything they can to do so. Being lean or muscular beyond a certain point is generally not consistent with that goal. Our bodies actively work to prevent it.

So I've become slightly more receptive to the idea of using drugs when there is simply no other way to solve the problem. This assumes that they are safe, effective, and affordable. Being legal, or at least in that gray area between legal and controlled is important too. Going to jail to lose a few pounds of fat or gain a few pounds of muscle is silly. So is throwing away your health or savings account, although people do both all the time. So my criteria for a good drug are that it should be inexpensive, available, effective, and safe (at least relatively speaking, there are risks with any drugs).

Ephedrine is a good example of a drug that meets my criteria. Although it's becoming less readily available, it is inexpensive, effective, and has a solid decade of research showing that it's safe if used properly. Injectable growth hormone (GH) is an example of a drug that doesn't meet my criteria. It's difficult to get, extremely expensive, doesn't really do that much, and has some problematic side effects.

This is a booklet about one of those drugs, a drug called bromocriptine, that meets all of my criteria. It's actually quite old and has been around for at least 3 decades. Bodybuilders used it in the 80's for reasons other than what I'm going to discuss in this book and I came across it while researching another topic. Looking more deeply into its mechanisms of actions, I realized that it allowed us to solve one of the more major body problems, which I'll discuss soon enough.

With that out of the way, I don't want anybody to think that I'm trying to become some sort of 'drug guru' with this booklet. It's bad enough that people think of me as the 'keto-guru' after my first book since I happen to know about and advocate a lot of different dietary approaches. Even then, people seem to think that all I like are ketogenic diets, or that I think nothing else works.

In any event, I definitely don't want anybody to be misled that I'm trying to become the next big drug expert because of this booklet. Training and nutrition physiology and how to manipulate them 'naturally' are still my primary interests and I'll leave the bulk of the drug study to the other experts. This is simply a tangential project on something I found very interesting. I hope you will too.

A couple of notes to readers

First and foremost, I should mention that bromocriptine is a prescription drug in the United States. Although it can be ordered from overseas without one, obtaining it legally in the US requires that you go to a physician and that he write you a prescription. And while bromocriptine is approved for several uses (primarily hyperprolactinemia, Parkinson's disease, and acromegaly), the FDA has not approved it for the uses outlined in this booklet. I should also note that it is legal for a doctor to prescribe any non-scheduled drug for any condition for which he feels it would be beneficial. Bromocriptine is not a scheduled or controlled substance, and falls into this category; a physician could prescribe it for the uses described in this booklet although they are not FDA approved uses.

Second, the major part of this booklet deals with a lot of underlying physiology to explain how and why bromocriptine works. Readers who simply want to know the bottom line details of how to use it should page ahead to chapter 7, and go back to read the first 6 chapters afterwards.

Finally, a note for the semantically nitpicky. Throughout this book I have chosen to use rather anthropomorphic terms to describe certain processes. I write of hormones 'telling' the brain what's going on, and the brain 'knowing' what's happening. Don't read too much into this or get your semantic panties in a twist.

I don't mean that a little hormone molecule is walking up to the brain and 'telling' it anything in the sense that you might tell a friend something. It's simply a shorthand way for me to say that 'a hormone travels through the bloodstream, binds to a receptor, causing a series of biochemical events to occur, which cause a series of things to happen'. When I say that the brain knows something, it means that it has some biochemical way of sensing or measuring changes elsewhere in the body, and adapting accordingly. It's simply easier to type and easier to read by writing 'tell' and 'know' even if they aren't literally correct. So deal with it.

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Chapter 1: Defining the Problem

I always seem to start out these projects with a chapter on defining the problem. I'm not entirely sure if it's for the reader's benefit or my own. Either way it serves the same purpose. I try to solve body problems by first defining what those problems are, then figuring out what's causing the problems, and finally seeing if they can be fixed in any effective fashion. This booklet will follow that pattern.

So let's define the problem very generally: Your body hates you. I know, I said this in the foreword but it bears repeating. It's become one of my more common catch-phrases and I am quite serious about it. Actually, that sentence has it backwards. Your body really loves you and wants to keep you alive. It's just that what it thinks is the right thing to do to keep you alive is generally contrary to your goals of less weight/fat and more muscle.

Let me get a little more specific with the problem: dieting sucks. That's the real issue and topic of this book. Anyone who's tried to lose weight/fat (there is a difference) and failed knows this to be true. Gaining weight is pretty easy for most folks, just eat and enjoy. Losing it is the real hassle. Sure, a genetically lucky few can do it without much effort but they aren't the ones reading this book. For good biological reasons, that you'll learn about next chapter, it's easier to gain weight than to lose it for most people.

I'm fascinated with dieting and fat loss. I have been for as long as I can remember. It's the psychological profile that comes along with being a former fat kid. I've done/read most of the diets out there, tried all of the supplements, even a couple of the drugs. All this was in the quest to be lean and stay there. "Why?", you ask.

I'll be honest: I want to fix myself. It's the same reason that nutcases become psychologists and fat girls become dietitians. They want to fix themselves, too. It's a common affliction. My friend Bryan Haycock, who has always wanted to be huge, has dedicated most of his time to studying muscular growth physiology for the same reason. He wants to be huge, so he researches muscle growth; I want to be lean so I research fat loss. He and I make a very good team, especially when you throw in our endocrinology-obsessed buddy, Elzi Volk. The three of us have most of it covered.

Even at 10% bodyfat, I'm not happy. I know I'm lean, healthy, all of that. My doctor is thrilled and thinks I'm nuts to want to be leaner; so does my mom. They may

not be wrong. But at 10% bodyfat, I'm simply not satisfied. The more athletic readers know what I'm talking about. Other readers may just think I'm nuts and obsessive. They may not be wrong either.

Losing weight/keeping it off

Although many overweight folks might disagree, losing weight or fat isn't fundamentally that difficult. Despite numerous claims to the contrary, no magic diet is needed and even fat folks can lose weight: just diet and exercise. There are two major obstacles, which are related. The first is sticking to the diet in the short-term. Hunger, deprivation, and anxiety all work against the dieter and most just return to their old habits because it's easier. The second is keeping the weight off in the long-term. Even a 5 to 10 pound weight loss in obese folks improves health indices, but keeping even that off for more than a little while is pretty rare.

Folks who want to get extremely lean without using drugs have to contend with additional issues such as muscle loss, crashing hormones and a host of other problems. This is a problem I've been looking at for years and there are few real or good solutions. Assuming they work at all, most of them are band-aid fixes, and none of those solutions are very permanent beyond 'Deal with it'. Drugs are the exception; drugs work wonderfully and solve many, many problems.

If that's the problem, what's the goal?

So, what are we trying to accomplish exactly? For the average person, losing weight and keeping it off without hunger and recidivism would be the goal. It sounds simple, really, but most people still fail miserably at it. For the obsessed and/or athletic, the ultimate goal would be losing all the fat you want without your body screwing you on the way down. In both cases, it'd be ideal if you could lose fat weight with no muscle loss, no metabolic slowdown, no crashing hormones, and no runaway appetite. If you could stay leaner without much effort that would be great too. If you're an athlete, being able to gain muscle without getting (too) fat would also be ideal.

It's not as simple as it sounds and most solutions to date have been only

marginally successful, except for drugs. Drugs work great because they allow us to step outside of our normal physiology (which you'll learn about soon). Most of the dietary or supplement strategies are aimed at correcting part of the problem; many try to mimic drugs and some actually succeed. Prohormones, anti-catabolics, fat-burners, appetite suppressants, protein powder, etc. are all attempts to fix some part of the overall metabolically screwed up picture. Even the best only work to a limited degree.

Even the weight loss drugs introduced by the pharmaceutical industry have only been marginally successful. They are either appetite suppressants (such as Phentermine, Fenfluramine, and Meridia), thermogenics which have side effects, or compounds which impair fat absorption (such as Orlistat, and runaway diarrhea is the price you have to pay). Typically these drugs cause a small weight loss, maybe 5-10% of total bodyweight, and then stop working (but see chapter 10 for a possible solution). They are all trying to fix a single part of the overall metabolic picture, without dealing with the real problem (hint: it's your brain).

Drug-abusing bodybuilders/athletes don't have the normal problems, since they are replacing their body's normal hormones with drugs. Steroids, thyroid medication, injectable growth hormone, cortisol blockers, and appetite suppressants are just a partial list of the chemical abuse that occurs in elite bodybuilding and athletics. Use of these drugs allow those folks to do things that aren't 'normal' relative to human physiology. The results also make natural athletes expect a lot more than is realistically possible; they wish they could pull off the magical body transformations without drugs, but they find out the hard way that it can't be done. Finally, use of all of these drugs can come at a high cost: financial, legal, and health-wise.

Ultimately, all of these drugs are used to fix individual parts of the picture without addressing the real problem. This booklet is about fixing the real problem, which turns out to be the brain and what it does to you when you're dieting. I don't claim to have the complete answer...yet. But as research builds up and we figure out what's causing the problem, we are getting closer to the answer. The drug bromocriptine, a very old drug with several uses totally unrelated to body composition, turns out to solve many of the problems that I talked about above. I'll present the data and mechanism soon. In addition, it's very safe at the doses needed, fairly inexpensive, legal, and not too hard to come by. So it meets my criteria for a good drug.

Before you get the wrong idea, this booklet isn't only aimed at the psychos like me, who want to maintain single digit bodyfat year round without all of the associated problems. The data I'm going to present turn out to apply to dieters in general, because the mechanisms at the heart of the problem is the same.

Contrary as it may seem, losing 10 pounds and keeping it off long-term is essentially the same as dieting to 'normal' bodyfat levels (11-18% in men, 21-28% in women) or getting even leaner. The difference is simply one of extreme. All three situations come with the same basic problems: hunger, metabolic slowdown, impaired fat burning, crashing hormones, all of which derail your efforts. The difference is merely one of degree: the person dieting to 'normal' isn't as badly off as someone dieting to 6% bodyfat. Since all of these problems ultimately stem from the same place (the brain) they end up having the same basic fix.

Really defining the problem, part 1

Ok, so the statement that dieting sucks doesn't really tell you much and the last section was pretty general. So let's define the problem in a bit more detail.

A quick look at the dieting literature shows an exceptionally poor rate of success. Depending on which data you believe, anywhere from 90% on up of dieters will gain back all of the lost weight within a few years. Some have even concluded that it's not worth attempting weight loss since nearly everyone will gain it back.

As I mentioned above, losing the weight/fat ultimately isn't the problem, keeping it off in the long-term is. Since losing it really isn't that difficult for the most part, current research is focusing more on how to keep the weight off. Eat less, exercise, and the weight usually comes off. Keeping it off long-term is the real problem, and it's where most people fail.

There are many, many reasons for this of course, some physiological, some psychological. Changing long-term behavior patterns is difficult for most people, almost regardless of what they're trying to change. And nobody really likes restriction even when it's self-imposed. Both cause anxiety which humans don't particularly enjoy, so we tend to revert to old habits. Those are some of the psychological reasons that dieting is so difficult.

Physiologically, dieting and weight/fat loss cause a host of other problems

which act to derail your efforts. Decreases in metabolic rate and energy/activity levels, along with a decrease in fat burning are par for the course when folks lose weight. Fat storage enzymes tend to increase as well, which means that the dieter's body is just waiting to start storing fat again when calories become available. When (not if) the diet is broken, the pounds come back on, frequently with a little bit extra stored for good measure.

The small percentage of dieters that do succeed long-term tend to show characteristic changes in things such as eating and exercise habit. Most use regular self-monitoring of weight or bodyfat percentage to prevent them from slipping too far and there are a few other strategies that come into play as well. Simply, successful dieters make these changes and maintain them long-term. They have to restrict calories to some degree for the rest of their lives to maintain the weight/fat loss. I suspect they're a little bit hungry and unhappy most of the time. But this describes a small minority; most people, miserable and anxious simply return to old habits and get fat again. An ideal solution would fix this problem.

Really defining the problem, part 2

It's convenient for weight loss 'experts' to blame weight loss failures entirely on a lack of willpower but that turns out to be a very simplistic (and not entirely correct) explanation. Quite literally, the dieter's brains are the real problem and are actively working to derail dieting success. Essentially, their brains 'want' them to be fatter and are sending powerful hunger and appetite signals to get those people to eat. That's on top of the other metabolic derangements, such as slowed metabolic rate and decreased fat burning, along with increased fat storage capacity, that occurs with dieting and weight/fat loss.

Dieting athletes and bodybuilders have a slightly different set of problems although they turn out to be related in terms of the mechanisms involved. For most, psychological issues aren't as big of a deal; most athletes equate suffering with progress in the first place. This is both good and bad. On the one hand, most athletes don't whine about being hungry or changing their habits, they accept it as part

athletes don't whine about being hungry or changing their habits, they accept it as part of the price of playing. At the same time, many confuse working harder with working smarter. What they lack in finesse, they make up for with pigheaded stubbornness.

The primary problems for very lean individuals are physiological. Without drugs (euphemistically referred to as 'props' or 'gear' in the subculture), natural athletes lose muscle mass at an alarming rate and have totally screwed-up hormone levels when they try to get very lean. Staying lean, except for the genetically lucky, is nearly impossible, as is making any real gains in muscle mass without gaining the bodyfat back. You'll learn why soon.

Getting lean beyond a certain point, in the range of 10-12% bodyfat for men and maybe 18-20% bodyfat for women, causes levels of testosterone, growth hormone, thyroid and the other 'good' hormones to crash. Levels of the 'bad' hormones such as cortisol skyrocket. Appetite soars through the roof. Muscle loss accelerates and getting rid of that last little bit of fat is a total pain as your body fights to keep you alive. For bodybuilders who only have to be lean for one day (contest day), it's no big deal. But stories of folks ballooning up after the contest are rampant. The physiology coupled with months of deprivation can lead to month long binges. As you might imagine, fat storage takes off.

As it turns out, nearly all of the problems I described above are being controlled by the same basic systems and they turn out to be mostly in the brain. Appetite, hormones, the psychological drive for food, fat burning, etc. are all under control of the same basic system at a fundamental level. And it's your brain that is screwing you over. This is why the suggestion to "Just try harder" doesn't get people very far. Your brain, which is feeding your urges about behavior, food, etc. is fighting against you. I told you that your body hates you. It does and, eventually, it's going to win.

The brain and setpoint

In the last five years or so, obesity research has exploded into a whole new realm. Rather than focusing on idiotic topics such as "Why fiber is good for weight loss" the current focus is on the biological mechanisms that drive eating behavior, maintain bodyweight at certain levels, and control the partitioning of calories (where they go after you eat them). It's been suggested for decades (since at least the 50's)

that the body tries to maintain some type of 'setpoint' level of bodyweight or bodyfat and will try to maintain that level. While that's a little bit simplistic, it turns out to be more true than not. Regulation of the setpoint is where the research is primarily focused.

Simply put (the details are coming later), the brain has sort of a preconceived notion of how fat it wants you to be, a setpoint as it were. A great deal of this 'setpoint' is imprinted at a very early age (1). Like when you're in the womb and the first few months of life early. Quite literally, what your mom did while she was pregnant is affecting you now. If she was obese (or, as it turns out, undernourished), you're more likely to be overweight and have trouble losing and keeping weight and fat off. You probably have more fat cells than you'd otherwise have, as well as a brain that 'wants' you to be fat. Other aspects of your physiology, such as your hormones, may also be imprinted while you're in the womb (2). All of these factors contribute to the difficulties people have in losing fat. So if you have problems with losing fat or with your hormone levels, just blame your mom. She should appreciate that.

In addition to your early childhood, what you did during puberty as well as what you do as an adult can affect setpoint. It looks like overeating for long periods of time or staying fat long enough can cause setpoint to go up (above where it was when you were born). Contrary to popular belief, you can also add fat cells if you stay fat/overeat for extended periods, and this may affect setpoint as well as your propensity to put fat back on after you diet. Pregnancy appears to raise setpoint a bit in women too. It's bringing setpoint back down that's the problem.

The whole setpoint concept is pretty easy to demonstrate in animals, although harder to measure in humans. You can readily breed rats who will avidly defend a given bodyweight/bodyfat setpoint. By defend I mean this: they adapt their physiology, metabolic rate, activity level, food intake, etc. in response to over- or under-feeding.

When you overfeed these rats, their metabolic rate increases, they become more active, and they automatically decrease food intake. This brings them back to their setpoint level where everything normalizes again.

In contrast, when you underfeed the same rats their metabolic rate decreases, they decrease their activity levels, and increase food intake (3), which brings them back up to their setpoint again. They make a useful model because scientists can biopsy their little rat brains and see what's happening chemically and figure out what's driving the process.

With both under- and overfeeding, rat brains show fairly characteristic changes that cause everything to occur. Once bodyfat is back to where it should be, their brains think everything is normal, and brain chemicals normalize.

You can also breed rats with a high setpoint to begin with. If you maintain them at a bodyweight that's lower than their setpoint, even if they aren't actively dieting, their brains and the rest of their rat physiology will show the same changes as if they were starving. As soon as you fatten them up to their setpoint, their brains go 'Aahhh' and everything becomes normal, at which point they start to defend that (higher) setpoint. A fed rat brain is a happy rat brain, or something like that.

Humans show some of the same tendencies as rats as well as the same basic neurochemistry. The big difference is that humans appear to defend against underfeeding much better than overfeeding. That is, overfeed someone and you generally don't see major increases in metabolic rate or decreases in hunger. There are exceptions, people who burn off extra calories through fidgeting and other activities; these are the people who tend to stay very lean and have trouble gaining weight (4). They also have appetites that shut off readily when they overeat. They are not most people and we hate them. The only pleasure we might derive in this regard is knowing that they will be the first to die if a famine ever comes.

In most people, when you overfeed, metabolic rate goes up a little and hunger decreases a little, if at all. Excess calories are stored as fat with excellent efficiency in most people except those lucky few who burn the majority off (4). To get far ahead of myself, these folks will likely turn out to be very leptin sensitive while everyone else will be found to be suffering from some degree of leptin resistance. This will make more sense in a chapter or two.

It's when you underfeed people that the problems start: hunger soars, metabolic rate and hormones crash, fat burning slows down, muscle loss goes up, fat storage capacity increases. It's during dieting that the real problems I talked about above start to occur. Your body hates you and defends better against underfeeding than it does against overfeeding. This actually makes good evolutionary sense.

What does evolution have to do with it?

Now you're wondering about that last sentence, how did being fat and

defending against underfeeding/starvation make good evolutionary sense? Even if you weren't wondering, I'm going to tell you. I have to justify the cost of this booklet somehow.

During most of our evolution, being fat up to a point was actually beneficial, because it helped us to survive when food was unavailable. Except in tropical environments, and up until very recently, that was usually about half of the year. People would typically fatten up during the summer, when food was available, to ensure that they could survive the winter when food wasn't around.

The increased bodyfat would give them the stored energy to get through the winter on top of helping to keep them warm. But being fat under these conditions wasn't a danger or risk, it was a benefit. It's only in recent times where being fat is a health risk, mainly because people get fat, and stay fat for extended periods. The normal starvation period that we evolved on, which leaned us out for half of every year, doesn't occur anymore. Modern life is one long fattening cycle (readers who are powerlifters can think of it as one long bulking cycle).

In contrast, being skinny meant that you tended to die when food wasn't available because you starved to death that much sooner. The folks who could best deal with starvation, by storing calories as fat efficiently when food was available and by slowing metabolic rate and all the rest when it wasn't, survived, and we carry their genes (5). This is called the Thrifty Gene hypothesis, in case you care.

To your body, dieting is fundamentally identical to starvation, it differs only in extremity. In both cases, you're eating less than your body needs and, in both cases, your body adapts pretty much the same. That is, your body doesn't 'know' that you're only dieting for 8 weeks to look good in a bathing suit. It only 'knows' that you're eating less, and adapts accordingly. You'll find out how it 'knows' in the next chapter.

While I'm on the topic, a little more bad news for female readers. We've known for years that women have a harder time losing and keeping off weight, no matter what they do. In addition to having a lower metabolic rate overall, women's bodies generally adapt faster and harder to caloric restriction or exercise than men's bodies do (6). To put it in the above terms, their bodies appear to defend against weight loss even more so than men's do. Oh yeah, they also don't burn off excess calories as well with overfeeding (4). As my friend Elzi Volk says "When it comes to fat loss, women are screwed."

Again, this makes evolutionary sense. Women were ultimately responsible for

the survival of the human race (since they give birth to and take care of the children), so the ones who could stay alive the longest during the winter famine were the ones who passed on their genes (7). This at least explains why women have a much harder time losing fat (and keeping it off) than men. The exact mechanisms by which women's bodies are able to do this are still under study. Figuring out what is the problem with women and fat loss and fixing it is one of my next projects. For now, just accept that it sucks to be female if you want to lose fat. You can do it, but it's more difficult.

Summary

The basic problem is this: your body appears to have a set idea of how fat it 'wants' you to be. That's your 'setpoint' and how high or low it is depends on what your mom did when she was pregnant, what you did during puberty, and what you've done as an adult. This causes your brain to set things up to try and keep you at that weight, more or less. To a degree, your body can adapt metabolism, fat burning, appetite, etc. up or down in response to over- and underfeeding respectively.

But, in general, for clear evolutionary reasons, your body works far harder against you when you underfeed than when you overfeed. Your body doesn't know that the next famine isn't around the corner, and thinks it's a great idea to keep you a little bit fatter just in case. If food becomes unavailable tomorrow, you'll live longer if you're fatter. In a few thousand years, once our bodies have figured out that annual famines aren't coming, maybe our genetics will adapt. Until then, metabolic slowdown, decreased fat burning, increased fat storage, hunger and all the rest are the price we have to pay for dieting.

In addition, in response to that famine, your body has an extremely well developed way of keeping you alive: slowing metabolic rate, making you less active so that you burn less calories, making you hungry as hell so you'll go look for what food might be available, decreasing fat burning, and many others. All are aimed at helping you to survive until food becomes available again. And, as far as your body is concerned, dieting is really no different than starvation. The only real difference is one of extreme, eating something versus eating nothing. In both cases, your body 'knows' that you're eating less than you should, and it adapts accordingly.

So how do we fix it? The first step to solving that problem is to figure out how the body is performing this trick, the mechanism: knowing you're starving and adapting. Then we see if we can do anything about it.

Chapter 2: How your body knows

So now you're wondering how the body manages this feat: how does it know when you're over- or underfeeding so that it can adapt accordingly? It's a question that has kept scientists busy for many years. Me too. It never made sense to me that your body would slow metabolic rate or fat burning or give up valuable muscle when fat was so abundant. And yet it does just that. Even at 170 pounds and 10% bodyfat, a male has about 17 lbs of fat, nearly 60,000 stored calories available. That's enough for 20 straight days of total starvation, much more if you're still eating (i.e. dieting, not starving completely). And it'll still use muscle instead. It made no sense.

I always figured that somehow the body could 'tell' how much you were eating by some signal from your stomach in relation to the amount of food you ate, and that it used that to judge how much you were (or weren't) eating. While there is a hormone, ghrelin, that is released from the gut in response to food intake, it doesn't turn out to be the signal that is really important. Two years ago, I found the part of the puzzle I was lacking which at least defined and explained the problem. Fixing the problem has been more difficult.

The problem, well a big part of the problem anyhow, turned out to be in our fat cells all along: our bodyfat was telling our brains what to do and how to adapt. This makes a certain sort of sense in hindsight, as so many things do. As our primary store of energy, bodyfat was ultimately determining whether we lived or didn't during the famines. It makes sense that bodyfat would contain the 'signaling' system to tell the body what was going on. Of course, it's not quite that simple, but it never is. Other systems play a role, but fat cells are the primary controller telling the brain what to do.

I should also mention that the full system(s) and mechanisms involved in bodyweight, appetite, and metabolic regulation are extremely complex and still under heavy research. But we know a few of the major parts and I can sketch the system well enough for you to understand the partial solution I'm going to describe in this booklet: the drug bromocriptine I've barely mentioned up to this point.

A tale of two hormones: insulin and leptin

I mentioned last chapter that your brain is a big part of what's controlling your body when you diet. This raises the question of how it knows what to do. Very basically, the brain is constantly receiving signals from the rest of your body regarding your bodyweight, bodyfat percentage, how much you're eating, how much you're exercising, and many others. It receives these signals in a variety of ways. One of the main ways, and the one we're concerned with here, is through changes in hormone levels. For the uninitiated, hormones are simply chemicals released by one cell in your body that have an effect somewhere else in your body.

So your your brain is receiving signals from the rest of your body via changes in hormone levels. At the same time, your brain is sending signals back to the rest of your body, via hormones and your nervous system, telling it what to do. Increase this, decrease that, change the other. The body tells the brain what's going on, and the brain is telling the body what to do about it. That's a little simplistic but it works for now.

Basically, we've got this huge feedback loop where the brain gets information from your peripheral tissues (e.g. fat, muscle) and your peripheral tissues get information from your brain (8). If it weren't complicated enough, those peripheral tissues are communicating with one another by those same hormones (9). Fat cells are talking to one another, and with your muscles, and your pancreas, and probably vice versa. They are all telling one another what's going on in the body, which determines what the body does about it. This all occurs through changes in hormones and various chemical messengers but there's a lot of communicating going on.

The main communication loop I want to focus on is between your peripheral tissues and your brain. The entire system is extremely complex and there are short- and long-term signals being sent to the brain via changing hormone levels, alerting it to what's going on in your body. Some of these hormones act in seconds, some in minutes, some in hours, some in days. It gives the body a great deal of adaptability and flexibility but it also makes the system a real pain to figure out or fix. Although there are literally dozens of hormones involved, in the context of this booklet, and the issue of bodyweight regulation (and related issues), we only need to be concerned with two of them (and really only one of them): insulin and leptin.

Although I assume that most readers know what insulin is, here's the brief rundown just to be safe. Insulin is a hormone released by the pancreas in response to carbohydrate (and to a much lesser degree protein) intake. While its primary role is as a storage hormone, putting calories into muscle and fat cells for later use, insulin appears to send the brain signals about your eating patterns. Injecting insulin directly into the brains of animals decreases hunger and appetite; the same system may play a role in humans as well (8). You can't inject insulin into human brains, of course, but increasing insulin levels after a meal may be one of several short-term signals telling your brain that it's time to stop eating.

Since insulin is very responsive to single meals, going up when you eat, and back down after a few hours, it mainly affects short-term responses to food: when to eat, when to stop eating, that sort of thing. As well, it's fairly easy to control, just make certain food choices and you can manipulate insulin pretty easily: fast digesting carbohydrates raise insulin quickly but it tends to crash afterwards; slow digesting carbohydrates raise insulin more slowly and keep levels stable for longer. I won't really talk about insulin that much more.

The second and probably more important hormone that concerns us is leptin. Although its existence was hypothesized back in the 50's, the actual existence of leptin wasn't proven until 1995 when the OB gene, which is the gene which tells the fat cell how to make leptin, was identified (10). The discovery of leptin literally changed the face of obesity research forever and several thousand papers on leptin have appeared since that time. None dealing with fiber or why it aids fat loss, thank god. So, what is leptin?

Leptin basics

Leptin is a hormone, a protein-based hormone (which means you can't take it orally) to be more exact. Although it's made in muscle, stomach and a few other places in the body, leptin is primarily made by fat cells. That's right, those nasty fat cells that you want to get rid of are producing one of the most important hormones in your body. It's turning out that nearly every tissue in your body has leptin receptors (10), which should tell you how far-reaching of an effect that leptin has on your body.

To say leptin affects everything isn't very much of an exaggeration. Once again, this makes a certain sort of sense. What your body 'decides' it can do is going to be

based on how much energy it has available. And how much bodyfat you have is a major determinant of how much energy you have stored. A signalling system that 'tells' your body and brain how much bodyfat you have makes perfect sense; in hindsight anyhow. That's what leptin is, the signalling system (well, the primary signalling system) telling your body what the status of your energy stores is.

As I said, leptin is mainly made by your fat cells. In fact, leptin levels show a frighteningly high (for a biological system) correlation with bodyfat levels. With a little bit of variance, having to do with where the bodyfat is located, higher bodyfat means higher leptin and vice versa. Visceral (gut) fat doesn't affect leptin levels as much as subcutaneous (under the skin) fat and there may be slight differences between different subcutaneous depots (i.e. abdominal vs. leg fat) but beyond that, total bodyfat is the biggest determinant of leptin levels. With few exceptions, more bodyfat means higher leptin levels.

Additionally, women typically have higher leptin levels than men. Depending on the study, women run anywhere from two to three times as much as leptin at the same bodyfat level. Women's bodies appear to adapt differently to changing leptin levels as well. This is most likely a huge part of why women adapt differently to weight loss than men.

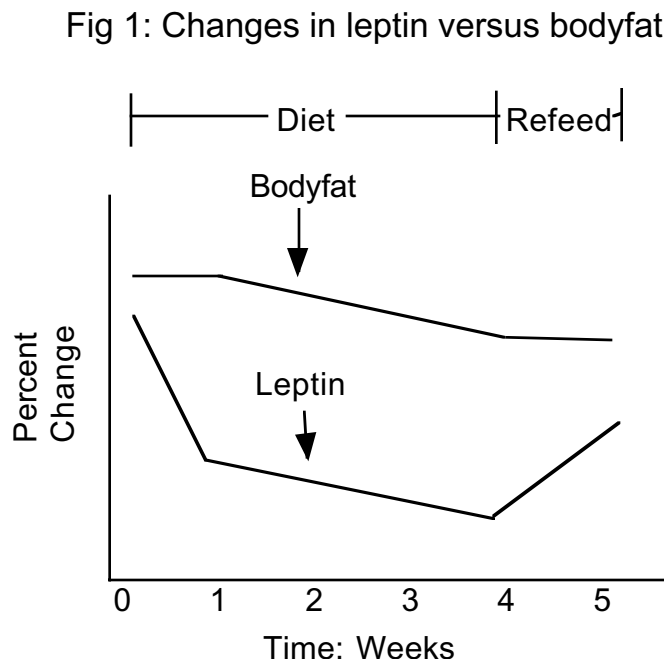
As it turns out, the brain has a lot of leptin receptors, in places that are involved in controlling appetite, such as the hypothalamus. Now we're starting to see the connection between the last chapter and this chapter. Basically, leptin 'tells' your brain how much bodyfat you have. Gain bodyfat and your brain knows about it because of the increase in leptin. Lose bodyfat and your brain knows about it because of the decrease in leptin. In fact, it was originally thought that leptin only 'told' your brain how much fat you had, and controlled appetite in response to changes in bodyfat. But it's actually more complicated than that. It always is.

In addition to being affected by total bodyfat level, leptin levels also change in response to even short-term over- and underfeeding. Go on a diet and leptin levels will drop by nearly 50% within a week. Of course, you haven't lost 50% of your bodyfat (wouldn't that be nice). Overfeed for a few days, and leptin comes up about as quickly; that is, faster than the bodyfat comes back on. I'm not going into details but it has to do with changes in glucose metabolism in the fat cell. Basically, the fat cell 'senses' whether you're storing or mobilizing calories, and that affects leptin production and release.

People who know me from the internet know that one of our solutions to date comes out of this research: cyclical diets with high-carb/high calorie refeeds every so often. By inserting a day or two of high calorie, high carb feeding, you bump leptin back up (without putting on too much fat) to help avoid some of the negative adaptations to dieting. Leptin dynamics also helps to explain why people who have been dieting for weeks, and then who break their diet, frequently find that weight/fat goes down at first; presumably leptin is going up faster than the body can store fat and causing good things to happen. I'll talk a little bit more about cyclical diets later in this book.

The point is that your brain has a pretty direct connection with not only your bodyfat stores, but how much you're eating, all via changing leptin levels. In essence, leptin 'tells' your brain two things: how much bodyfat you have, and how much you're eating (11). How much you're eating determines the short-term changes in leptin levels; how much bodyfat you have determines the long-term changes in leptin levels.

So go on a diet and leptin levels will drop by 50% in a week, even though you haven't lost 50% of your bodyfat. After that point, leptin will go down more slowly, in conjunction with bodyfat loss. With short-term refeeding, leptin levels will go up more quickly than bodyfat (bodyfat may even continue to go down). This is shown schematically in Figure 1 below, representing dieting from weeks 1 to 4 and refeeding (eating at maintenance levels or higher) from week 4 to 5.



Time: Weeks

And, as I mentioned above, your brain reacts to decreasing leptin levels far more than it does to increasing leptin levels. It also looks like women's leptin levels may drop faster than men's and that their brains respond to decreasing leptin more/differently than men's which is probably part of why women have a more difficult time losing fat. Tangentially, we're (we equals Elzi Volk and I) are still working on figuring out exactly how women's brains perform this trick, adapting harder to changes in leptin levels, to see if we can fix the problem once and for all.

To state it as clearly as possible, leptin does not exist to prevent obesity, somewhat contrary to popular and even scientific belief. To paraphrase one researcher, if preventing obesity is leptin's role, it's one of the most ineffective hormones in human history. More accurately, leptin is an anti-starvation hormone, that tells your brain and body how and when to adapt in the face of reduced calories or increased activity (12). Anything that causes you to burn more calories than you're eating makes leptin go down, telling your brain and body what's going on.

I do want to make it very clear, although I'm not going to go into much detail in this booklet, that leptin does far far more than just tell the brain what's going on (13). Remember how I said that the tissues in your body are communicating with one another? Leptin is one of the many ways they do this. Leptin from your fat cells affects insulin release from your pancreas, and fat burning in your muscles. It also helps the hormones in your stomach (such as cholecystikinin or CCK) blunt hunger better and is involved in immune system function (now you know why you get sick more easily when you diet). Leptin may even be able to cause the permanent deletion of fat cells, a process called apoptosis (which just means cell death). More on that later.

A critical level of leptin appears to be necessary to trigger the onset of puberty, which is why undernourished children hit puberty later (and fat kids tend to hit it sooner). During pregnancy, extremely low levels of leptin may cause birth defects because the fetus 'knows' that there aren't sufficient calories to build everything, so only major stuff like brain and organs are built ; arms and legs, being less necessary, don't form. On it goes and an entire book could and should be written about leptin. For now just accept that it's really important.

Quite literally, the amount of bodyfat you have, and the amount that you're eating (both of which determine leptin levels) tell the rest of your body what to do and what it can do, controlling many (if not most) of the adaptations that occur with dieting. If you don't get anything else from this chapter, just burn that last sentence into your brain.

Summary

So now you know the basics of how your body and brain know what's going on with your bodyfat level and caloric intake; how it knows when you're dieting/starving or overfeeding. Changes in insulin (short-term, as in a few minutes to a couple of hours) and leptin (short-term meaning hours to days and long-term meaning weeks) signal your brain to let it know what's going on with your fat stores. When you eat less and lose fat, your leptin levels go down. This tells your brain that you don't have sufficient energy and it causes your body to adapt accordingly. When you eat more and gain fat, leptin levels go up. This tells your brain that your energy intake is fine or increasing, and your body may adapt a little. Since your brain isn't as concerned if you put weight on, it doesn't adapt nearly as much to overfeeding as to underfeeding. Losing weight/fat beyond a certain point scares your body and your brain, which thinks you're starving to death, and everything slows down to compensate. I told you before but this seems a good time to repeat it: your body hates you.

So that's the basics of the system, what leptin is, and how it tells your brain what's going on. The next question we need to tackle is a little bit more technical data regarding leptin, in terms of how it works in the brain, and what it does. This will finally lead us to the main topic of this book: bromocriptine.

Addendum: Ghrelin, the new pain in the ass

Since publishing the e-version of this booklet, I've looked more into the hormone ghrelin, and it looks like it is very important to the overall scheme of bodyweight regulation. Ghrelin is produced in the stomach, going up when you don't eat, and going down when you do eat. It also appears to interact with the same area of the brain where leptin is sending its signals (13a).

So when you eat less, there's a double whammy: leptin levels fall and ghrelin levels go up. Both affect the hypothalamus telling your body to adapt to dieting. Eating more causes leptin to go up, and ghrelin to fall which helps to tell your body that you're eating enough.

Chapter 3: Leptin resistance

At this point, you know a few things. The first is that there's a hormone called leptin, made by your fat cells (and a few other tissues) that acts as a primary signal in bodyweight/bodyfat, appetite, and metabolic regulation. On top of many other functions in the body, leptin's main role is to tell your brain two things: how much bodyfat you have and how much you're eating. The brain senses changes in leptin levels which is how it knows what's going on.

Those changes are what tell your brain and body how to adapt, shifting metabolic rate, fat burning, appetite, etc. up and down in response to over- and underfeeding respectively. Tied in with that, you already knew that your body adapts more to underfeeding than to overfeeding.

Although other signals are involved, the drop in leptin with dieting is one of the major causes of many of the problems we've discussed so far: increased appetite, crashing hormones, crashing metabolic rate, etc. It's not the only cause, of course, but it is one of the main ones.

If this all sounds new to you, you skipped the last chapter by mistake. The point to understand is that dropping (or simply low) leptin levels are one of the main signals that makes your brain 'think' you're starving to death. Your body adapts accordingly. At this point, you're probably asking yourself a fairly straightforward question, so I'll address it now. It makes a nice segue into this chapter anyhow.

Why not just use leptin?

So you're wondering: If dropping leptin is causing the body to adapt to dieting, why not just use leptin to fix it? A good question and there are a few reasons why using leptin itself isn't really workable.

The first is simply cost and availability. Leptin was never made available for public or medical use, and is currently only available for research purposes. Even if you could wrangle it from a chemical supply house, an effective dose (~0.3 mg/kg per day for those who want to know) would cost roughly \$1000 per day. That makes

growth hormone (GH), at about \$500 per month, a bargain by comparison. So we've got a ridiculously high cost and poor availability, not a good drug in my book.

The second problem is that leptin is a protein (peptide) based hormone. You can't take it orally because it will be broken down by the stomach; it has to be injected to be effective. Hardcore athletes and bodybuilders couldn't care less about this of course; injecting drugs is no biggie for them. But for the general public, an injectable drug isn't going to get very far. This is one of the major reasons leptin never got out of the research stage.

Insulin dependent diabetics, for example, who must inject insulin multiple times per day, don't do it because they enjoy it (and researchers are trying to find non-injectable insulin solutions for these folks). They do it so that they don't die. Developing an injectable drug for obesity was a losing proposition from a commercial standpoint.

The final problem, and the one that ultimately kept leptin from being developed for public use (which would have brought price down) is that it didn't really work for the most part. That's actually not entirely true, in some populations, at high enough doses, it worked a little, blunting appetite and causing weight loss (14-16). And although it hasn't been tested in extremely lean individuals (why bother?), it should work based on what we know about the system. The cost makes it unusable for that group anyhow. Also see the chapter addendum for details on a very recent study.

But the fact that it didn't really work in the target population (obese folks) is probably the main reason why it was forgotten. Obesity researchers and drug companies want drugs that work great and make them a lot of money. An expensive, injectable based drug that only worked a little didn't interest them because it wouldn't have sold well. So they gave up and moved on. Be glad that I didn't. Manipulating leptin and its effects turns out to be one of, if not THE key to fat loss and obesity.

So this raises the next question: if everything I talked about in the last chapter is true, and falling leptin is what screws us when we diet, why didn't injecting leptin work? To answer this question, I have to delve into more detail than I suspect most people want but that's life. It'll help you understand the solution, so make sure to read it.

Leptin transport

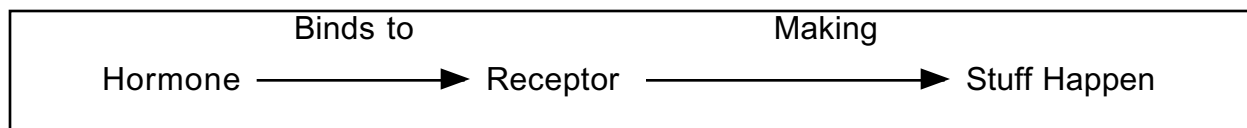
I explained to you that leptin is a hormone. And that leptin, through its interaction with the brain, causes many things to change: metabolic rate, fat burning, hormones, appetite, etc., etc. In explaining things that way, I left out a few crucial steps, mainly an explanation of how leptin does what it does.

Let's get silly. Imagine you're a leptin molecule floating through the bloodstream. You may be interacting with various tissues (such as fat cells or muscle cells) in the body. How does this interaction occur? It occurs the same way that all interactions occur, through receptors.

All hormones send their signal, to do whatever it is that they do, through receptors. Generally, these receptors are specific to a given hormone. The usual metaphor is of a lock and a key. The receptor is the lock, the hormone is the key. And only a specific key, the hormone, can bind a specific receptor, the lock. It's actually not that simple and some receptors can bind more than one hormone but you get the general idea.

So there are insulin receptors which only bind insulin which causes things to happen such as increased glucose uptake and glycogen storage (and a host of others). Androgen receptors bind testosterone, and a couple of related molecules, which causes things to happen such as increased protein synthesis. Estrogen receptors bind estrogen which causes things to happen such as increased fat storage. I could keep listing them but you get the point. The general way that hormones work is shown *very* schematically below in Figure 1.

Figure 1: How Hormones Work



Predictably, leptin works through a specific leptin receptor. So you, as the molecule of leptin floating around, eventually run into a leptin receptor and attach yourself to it. This makes stuff happen. For now, I'm not going to explain how binding

to the receptor makes stuff happen, just take it on faith.

So if you ran into a leptin receptor in the pancreas, you might send a signal telling the pancreas to release less insulin. If you ran into a leptin receptor in a muscle cell, you tell it to burn more fat and store more glycogen. You get the idea.

But what about the brain? For leptin to do its job in the brain actually requires an additional step compared to other tissues. First leptin has to get from the bloodstream into the brain (technically the cerebro spinal fluid or CSF, which is the fluid which surrounds the brain). This means getting across something called the blood brain barrier (BBB).

The BBB exists to make sure that only certain substances get into your brain, while keeping others out. Fatty acids, for example, can't get into the brain, because they can't get across the BBB. This is why they can't be used for energy in the brain. Ketones (made from fatty acids) and glucose can get across the BBB which is why they can be used for energy. Many amino acids cross the BBB and get used for the synthesis of neurotransmitters in the brain. Many drugs (such as cocaine) can get across the BBB as well, which is one of the ways that they exert their effects.

In the case of leptin, there is a specific leptin transporter that must be present in the BBB for leptin to get across. For various reasons, discussed below, this transporter can become defective, especially in obesity (17). Although there are probably genetic causes of leptin transporter defects, there are other factors which can affect transport as well. What this means is that not as much leptin can get into the brain to exert an effect. Aha! Now we have a potential reason why injecting leptin into fat folks didn't work; they may have had a defective leptin transporter so that the leptin couldn't get into their brains. Unfortunately, it gets even more complicated than that. It always does.

Leptin and two kinds of mice

For the next part of this chapter to make sense, I have to make a quick tangent and tell you about a couple of the most commonly used mouse models of obesity, since they are among the most heavily studied. They've also been responsible for most of the discoveries regarding the leptin system.

I mentioned last chapter that the discovery of leptin occurred when researchers

discovered the OB (obesity) gene. As with most discoveries in the biological sciences, this first occurred in animal models, mice actually. For decades, researchers have been looking at something called the OB mouse. Among other things, the OB mouse is obese, has a low metabolic rate, decreased fat burning, totally screwed up hormones, eats constantly, sits around a lot and has a number of other severe metabolic defects. Metabolically it looks like an obese human, just furrrier.

As it turns out, the OB gene is what tells the fat cell how to make leptin. OB mice have a defect in the OB gene so they don't make any leptin. None, zero, zilch. No matter how fat they get, they have no leptin in their systems. This means that no matter how fat they get or how much they eat, their little mouse brains always think that they are starving. So all of the adaptations to starvation that you'd expect are constantly running.

Fixing the problem is exceedingly easy: inject an OB mouse with leptin, and his appetite shuts off, metabolic rate and fat burning crank up to where it should be, hormones normalize, he loses fat like crazy and everything else corrects itself (18). Metabolically he is now normal. He is a happy well adjusted mouse, whatever that means in mice terms. Basically, the brain of the OB mouse is fine, but their fat cells don't produce the signal that's needed.

When researchers discovered this and figured out that the OB gene told the fat cell to make leptin, they figured for sure that obese folks would turn out to be just like the OB mouse: leptin deficient. This led to much shouting of 'Eureka', the filling out of patent applications for a leptin drug, and expectations of a ton of money. Oh yeah, and obesity cured because we're about helping folks, not just getting rich. Amgen, one of the major drug companies, paid an assload of money for the rights to leptin, figuring it would make them billions in returns.

So researchers took the next step and measured some humans and found exactly the opposite of what they expected: fat folks had tons of leptin floating around. Obese humans were NOTHING like the OB mouse. Shouts of joy turn to curses, patent applications are useless, gotta take back that new car because we're not getting rich afterall. Amgen was screwed.

I should mention that a few humans have been found who don't make any leptin at all. That's a few out of thousands of people measured. And several of those were in the same family, sharing the same genetic defect. These people have

voracious appetites and gain fat at an incredible rate; they are obese at childhood but don't hit puberty. Injecting leptin into them solves the problem. Unless you were several hundred pounds by the time you were two and never hit puberty, you are not leptin deficient; you're just fat.

So researchers had a problem, the OB mouse has no leptin and shows many of the characteristic defects seen in human obesity. But obese humans have plenty of leptin. So they went looking for a better model, and started looking at something called the DB (DB stands for diabetic) mouse. Like obese humans, the DB mouse has plenty of leptin, but shows many of the same defects seen in the OB mouse: obesity, low fat burning and metabolic rate, and all the rest. Additionally, the DB rat is profoundly diabetic, having elevated blood glucose, triglyceride and insulin levels along with the rest of the diabetic syndrome.

That is, both the OB and DB mouse look quite similar: low metabolic rate, lots of bodyfat, most of the same metabolic problems. But while the OB mouse has no leptin, the DB mouse has plenty. It even turns out that the DB mouse has leptin in its cerebrospinal fluid so the leptin transporter is working too. But the signal isn't being sent to the rest of the brain. So there's leptin present, the transporter is working, but nothing is happening. Why? If you guessed that the leptin receptor was the problem, you guessed right.

Back to the leptin receptor

Leptin receptors are found in a variety of places in the brain, mainly those areas involved with appetite control (primarily the hypothalamus for the neurology geeks out there). When leptin binds to those receptors, it makes stuff happen (as per my diagram a few pages back).

As it turns out, there are actually six different types of leptin receptors that have been identified. We only need to worry about two of them: the long form receptor and the short form receptor which are referred to as OB-RL and OB-Rs, respectively. Currently, it looks like the OB-Rs is involved in leptin transport into the brain but the OB-RL is what's important for leptin to have an effect in all of the other brain areas (19).

The DB gene is what tells the body how to make the OB-RL. Because of the

defect in the DB gene, the DB mouse only makes the OB-Rs, but not the OB-RL. So while leptin can get into the brain (via the OB-Rs), it has no effect because of the defective OB-RL. The transporter is fine but the receptor isn't working at all. And there's nothing you can do to fix it. Since the DB mouse's brain is totally unresponsive to leptin, injections don't have any effect. In scientific terms, the DB mouse's brain is completely leptin resistant because of the receptor defect. This brings us to the next tangent.

Hormone resistance

The DB mouse is an extreme case, where absolute leptin resistance has occurred due to a severe genetic defect. It's quite rare to see complete resistance to any hormone in humans, although it does happen from time to time. For example, there is a weird disease called androgen insensitivity syndrome where biological males never develop male characteristics because their androgen receptor is completely broken (resistant). Biologically they are males, but they look like females because androgens couldn't do their job in the body.

As with the OB defect (no leptin production), only one or two cases of such a leptin receptor mutation, causing complete leptin resistance have been found to date. As above, unless you were 200 pounds by the time you were a year or two old and never hit puberty, you're not one of these folks; you're still just fat.

So complete leptin resistance is an extreme rarity in humans, representing a severe genetic defect. However, relative hormone resistance, where a receptor doesn't respond very well to a hormone is something that definitely does occur in humans. In simple terms, receptors vary in how sensitive they are to a hormone.

That is, for a given level of hormone, you see different levels of stuff happening. If the receptor is highly sensitive, a small amount of hormone will have a large effect (lots of stuff happens). If the receptor isn't sensitive (it is resistant), a large amount of hormone will have little effect (not much stuff happens). This is yet another reason that the 'stuff happens' step in my diagram can get messed up. If the receptor is insensitive to a hormone, that hormone won't send as large a metabolic signal when it binds. When the receptor is resistant, less stuff happens.

An example that most people are probably familiar with is insulin resistance. In

insulin resistance, despite lots of insulin being available, the receptor doesn't work very well. So less stuff happens when insulin binds and you have to keep increasing the amount of the hormone to get an effect. And while some of this is related to lifestyle (diet, exercise, carrying too much bodyfat, etc.), some of it is genetic. People can vary ten-fold in their sensitivity to leptin, even at the same bodyfat level, because of differences in their genetics.

Related to this issue, it turns out that there is another strain of mouse, called the FA mouse which does show partial leptin resistance. That is, unlike the DB mouse which is 100% leptin resistant (no amount of leptin will have an effect), the FA mouse is only partly resistant. Leptin can still send a signal, it just doesn't send a very good one. Unlike the DB mouse which becomes obese almost from birth, the FA mouse becomes obese as it ages. With age it also becomes leptin resistant. This is much closer to what happens in humans.

It won't be surprising to find that people vary in leptin resistance as well, just as they vary in insulin resistance. In fact, it would be surprising if it weren't the case. It will most likely turn out that being genetically leptin resistant predisposes you to becoming fat, given our modern lifestyle of crappy food and no activity. Researchers have already identified folks who are predisposed to becoming obese, who show relatively lower metabolic rates, fat burning, etc. If it hasn't happened yet, they will most certainly be found to be somewhat leptin resistant already. The folks who are genetically lean, who burn off excess calories at an incredible rate (remember them from the last chapter) will turn out to be very leptin sensitive.

So now you take one of these folks who is starting out a little leptin resistant to begin with and give them the standard American diet (high calories, high fat, easily available and tasty) and couple it with low activity levels. These obesity predisposed people will gain fat more quickly compared to others. As they get fat, they will become more leptin resistant, making it easier for them to get even fatter. Eventually, their brains will adapt and shift their setpoint upwards, which makes it that much harder to lose the weight again. It's a vicious cycle.

This is basically identical to what happens in insulin resistance: folks starting out with genetically poor insulin sensitivity (i.e. higher insulin resistance) tend to put calories into fat cells more effectively than people with better insulin sensitivity. As they get fatter, they become more insulin resistant, making them more prone to gaining fat, which makes them further insulin resistant. Around and around it goes.

Anyway, partial leptin resistance would help to explain the studies I mentioned at the start of this chapter, where increasingly high doses of leptin were able to have an effect on bodyweight, appetite and the rest. With a high enough dose of leptin, you can overcome the partial resistance and get a small effect. Basically, the problem in most overweight humans is not a lack of leptin; there's plenty around. The major problem appears to be one of leptin resistance. There's another problem I address in this chapter's addendum.

As another complication, it appears that leptin transport across the BBB can become saturated, which means that no more can get across no matter how much is there. So say that the leptin transporter in the BBB saturates at 20 whatever (the units aren't important) of leptin. Once leptin levels reach 20 whatever or higher, further increases don't do anything: the system is maxed out. Jacking more in with a needle has no further effect because the transporter is maxed out. Extremely fat people have saturated their leptin receptors; putting more in can't have an effect.

In scientific terms, the phrase leptin resistance is being used to refer to both transporter problems and receptor problems. Since measuring leptin resistance in humans isn't as easy as in mice, scientists just lump transporter and receptor defects together and call it 'leptin resistance'. I'll do the same.

A mid-chapter summary

The main point I want to get across with all this technical blathering is that there can be two general explanations of problems with leptin (this is important, so pay attention) in terms of negative metabolic adaptations. In the case of the OB mouse, the transporter is fine; so are the brain receptors. But no signal is being sent because there is no leptin present. Although there are few humans who are completely devoid of leptin, very lean individuals have such low levels that it might as well be zero. Below 10% bodyfat in men, for example, leptin levels are very nearly zero.

In the case of the DB mouse, there is plenty of leptin floating around, the transporter works, but the receptor is completely broken. A handful of cases of complete leptin resistance have been found in all of the world, and they were all in the same family. So the DB mouse isn't really like humans at all.

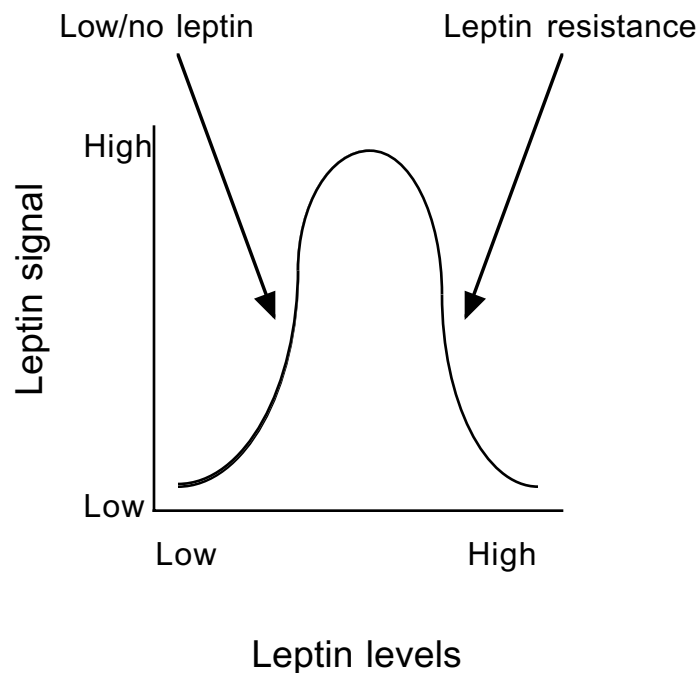
In the case of the FA mouse, there is plenty of leptin, the transporter works, but

the receptor is resistant and only works ok. And it works less and less well as the mouse ages. Which is a lot closer to human obesity (most people get fatter with age) than anything else we've looked at.

But regardless of the cause, in all three cases we get the same basic end result: less stuff happens. Since the brain isn't getting a signal from leptin, the body shows the same depressed metabolic rate, increased appetite, predisposition to gaining bodyfat, etc. It's just happening for different reasons.

In the first case, there is no (or low) leptin. In the second, there is a totally resistant receptor. In the third, there is a partially resistant receptor. The first and third cases are most similar to lean athletes/bodybuilders and obese folks respectively. If you're having trouble picturing this, check out figure 2 below. In both the case of low/no leptin or leptin resistance, the stuff happens step is decreased. We get the same result from different causes.

Fig 2: Low leptin vs. Leptin Resistance



Anyone familiar with diabetes may recognize a parallel between Type I diabetes (the receptor is fine, but the body doesn't make insulin) and Type II diabetes (there is plenty of insulin around, but the receptor is resistant and doesn't work well). In both situations, the end result is basically the same (reduced or absent insulin signalling),

but the cause is different. If you get nothing else from this chapter, remember the next sentence: different causes can yield the same result. Because the fix ends up being the same.

The DIO rat

To complete the picture I've been drawing you of potential problems in the leptin system, I need to switch from mouse to rat and talk about one more animal model, the DIO rat. DIO stands for dietary induced obesity, and refers to an otherwise normal rat who gets fattened up on a diet of high calorie, tasty, high fat food (basically cookie dough) and no exercise; which is a lot like our modern American lifestyle. Over time, this otherwise normal rat gets fatter and fatter, raising leptin levels higher and higher.

As leptin goes up and up, eventually its little rat brain becomes leptin resistant. It may be a transporter defect, or a hypothalamic receptor defect, or both. The exact reason why doesn't really matter. In response to constant pounding by high levels of leptin, the receptors stop working as well and a lower leptin signal gets sent. As above, this is identical to what happens in insulin resistance, on top of whatever genetic effects are present, chronically high levels of insulin cause the receptor to become resistant over time. Over time, the DIO rat will start to defend its bodyweight/bodyfat level at higher and higher levels (setpoint goes up) as the brain itself adapts. It looks like there may be permanent neural changes occurring which may be why setpoint can't be brought back down.

Finally, we have a model that sounds like what happens in humans: couple a poor diet with little exercise, and you get increasing bodyfat and leptin resistance. The difference being that some humans (which researchers call obesity prone) are probably starting off a little leptin resistant to begin with. Their lifestyle just makes it worse.

But just because it sounds similar, does that mean that it works the same way in humans? That appears to be the case. While absolute leptin resistance in humans is very rare, cases of partial leptin resistance in humans have been documented and seem to occur in members of the same family, along with obesity (20,21). This suggests that obesity/fat gain and leptin resistance go hand in hand, which is no real shock. It also means that leptin resistance has a genetic component

as well. No real surprise there either. Whether the leptin resistance caused the obesity or the other way around is a little harder to tell but it sort of doesn't matter.

As I described above, the cycle probably starts with slightly reduced leptin (or insulin) sensitivity due to genetic causes. Couple those genetics with the typical American/modern lifestyle and you get increased fat gain which makes the problem worse, in a vicious cycle. Of course, ultimately, the cause of the problem isn't the important issue. We just need a fix.

Leptin resistance is currently a big area of research in the field of obesity treatment. In addition to looking for drugs that might improve leptin sensitivity (i.e. decrease resistance), researchers have looked at the factors that affect leptin transport and/or sensitivity in the brain. Here are a few of them.

High fat diets appear to increase leptin resistance (22) although fish oil supplements may decrease leptin resistance given enough time (23). Alpha-1 agonists (drugs that stimulate the alpha-1 receptor) appear to increase leptin transport across the BBB (24). This may explain why the supplement synephrine (an alpha-1 agonist) affects appetite and fat loss, as well as why exercise blunts appetite (exercise raises levels of hormones which activate the alpha-1 receptor in the brain). I already mentioned the FA mouse, but aging is also associated with leptin resistance (25,26) and it's likely that this also occurs in humans. This helps to explain part of the age-related increase in bodyfat along with problems in regulating appetite: our brains are becoming leptin resistant as we get older. Did I mention that our bodies hate us yet this chapter?

Summary

Ok, now you have a basic understanding of how leptin sends its signal to the brain. Leptin is released from the fat cells, floats around in the bloodstream (where it also binds to receptors on tissues all over the body), gets carried into the brain by a specific transporter where it binds to specific receptors on neurons in the hypothalamus. This causes stuff to happen. I'm still leaving out a few steps but I'll get to those in a chapter or two.

I also told you about a bunch of different animal models of obesity, all of which share the same basic problems to one degree or another. The OB mouse produces

no leptin at all although its brain still responds just fine. Although a complete leptin deficiency is exceedingly rare in humans, very lean individuals have leptin levels that are low enough to be considered zero.

The DB mouse produces leptin just fine and even has a working leptin transporter. However, it has a defect so that it doesn't make the right receptor for leptin to bind to in the hypothalamus and no leptin signal can be sent. It is completely leptin resistant. As with complete leptin deficiency, only a very few cases of complete leptin resistance have been found in humans.

The FA mouse has only a partial defect in the leptin receptor. So leptin can send a signal, just not a very good or strong one. The FA mouse is partially leptin resistant which is a lot closer to what goes on in humans (unlike the DB mouse).

Finally there is the DIO rat, a rat made fat with a poor diet and no exercise. As it gets fatter, it becomes leptin resistant and its setpoint goes up so that it defends higher and higher bodyfat levels. Of all the models, the DIO rat is probably closest to what happens in most cases of human obesity, except that humans predisposed to obesity are probably starting out with some amount of leptin resistance.

In humans, leptin resistance appears to be partly genetic and partly environmental, like just about everything studied to date. Some folks are probably born somewhat leptin (and insulin) resistant, which makes it more likely that they will get fat if you feed them a crappy diet with no exercise. As they fatten up, this will make them more leptin (and insulin) resistant, predisposing them to greater fat gain, which makes them more leptin resistant, etc. Eventually setpoint is shifted upwards in the brain.

When these folks diet, and leptin drops, their brains go into the same starvation mode, slowing metabolic rate and fat burning, increasing hunger and all the rest. It simply does so at a higher setpoint than normal, because of their previous lifestyle and/or genetics.

The main point I want you to get from this chapter is that both low/no leptin and leptin resistance ultimately cause the same end result: no or a decreased leptin signal being sent to the brain. The 'stuff happens' stage, a normal metabolic rate, normal fat burning, controlled appetite levels and a regulated bodyweight/bodyfat level either don't happen or don't happen as well as they should. So finally, we know the problem. What's the solution?

Using leptin would seem to make the most sense but I already explained why

leptin is ultimately unworkable. For lean folks, injectable leptin would probably work wonderfully but its price and availability makes it unusable in that regard. For obese folks, injectable leptin won't work anyhow, because of leptin resistance. Although see the addendum below.

The solution is to trick the brain into thinking you're not starving, while avoiding the issue of leptin resistance (27). Basically sending it a fake signal, the same signal that leptin would normally send but isn't sending, in some form or fashion.

Researchers have done this in the lab already in a couple of ways (28,29) but neither compound fulfills my requirements for a safe, effective, inexpensive drug. The first (Axokine, a derivative of ciliary neurotrophic factor) is injection only, the second isn't commercially available anyhow. The partial solution, the chapter of this booklet, and the topic I'm finally ready to tell you about is this: bromocriptine.

Addendum: Leptin injections finally work

Although I made it sound like the reason leptin didn't work was entirely because of leptin resistance and receptor saturation, this isn't entirely the case (I was trying to avoid confusing people even more). An arguably bigger part of the problem is that researchers were using it incorrectly. Actually, they were using it about how you'd expect.

Recall from a chapter or two back that leptin doesn't exist to prevent obesity. Neither does it exist to cause weight/fat loss. Rather, it is an anti-starvation hormone that tells the brain to adapt to lowered calories.

What this means is that increasing leptin above normal isn't necessarily the right approach except maybe in very lean people. Instead, the goal should be keeping leptin from falling during a diet. Understand the distinction here? Rather than trying to raise leptin above normal levels, the goal is to keep leptin from falling during weight reduction/dieting.

Now, I knew this two years ago and one researcher had made mention of it, but nobody followed up. Finally, this year, someone tried using leptin during a diet (29a).

In this study, four subjects were first dieted to 10% below their normal weights and measurements of leptin, thyroid hormones, and metabolic rate were made. As is typical of these types of studies, weight/fat loss caused a reduction in levels of thyroid hormones and metabolic rate.

Then, for five weeks, they were given twice daily low-dose leptin injections to bring leptin levels back to their pre-diet levels and measurements of thyroid hormones, metabolic rate, and body composition were made again. Low-dose leptin injections reversed the drop in thyroid hormones and metabolic rate, and caused further fat loss even though calories were still at maintenance.

This study points out a few things. First and foremost, it's some of the most direct evidence that leptin is part of the mechanism for adaptation during dieting in humans. Second, and perhaps more importantly, it points out that maintenance of leptin (or the leptin signal) during a diet is key to avoiding adaptations.

Now, I still don't expect leptin to ever be used as an obesity drug. There's still the injection problem. Even if it works wonderfully, injectable drugs are just too much of a hassle for most people. More importantly, drug companies and obesity experts (and dieters) really want a drug that will *cause* weight/fat loss by itself. A drug that only works with a diet and/or exercise program just isn't appealing because most people are lazy. Leptin doesn't meet that criteria (neither does bromocriptine, by the way); it only works if you're already dieting/exercising and losing fat.

Chapter 4: Bromocriptine

And finally, we come to the actual subject of this book: the drug bromocriptine. Most of the preceding pages were simply explanations of what's going on in the body so that this and subsequent chapters would make more sense. I should mention outright that I didn't come to the idea of using bromocriptine directly. It wasn't as though I was working through the preceding information (a topic I've been researching for two years) and had an 'Aha, bromocriptine will fix this!' type of moment. That's not how my brain works.

Rather, I came to bromocriptine from two different directions. The first direction was the topic of all the chapters so far: the details of how leptin is making 'stuff happen' in terms of overall metabolism, and how plummeting leptin screws us when we diet. For the most part, I had ignored the detail steps (represented in my 'how hormones work' graphic by the arrow between 'receptor' and 'stuff happens'). It wasn't that important and I didn't see any real way to control it. When I can't think I can affect something, I tend to ignore it. As it turned out in this case, I happened to be wrong that the system couldn't be affected.

In looking at another topic, that of fat cell apoptosis (a techie word for cell death), I came across an oblique reference to bromocriptine, mentioning that bromocriptine administration mimicked some of leptin's effects in terms of killing off fat cells. That is, in animal models, bromocriptine administration has many of the same effects as leptin is having (causing fat cell death, increasing metabolic rate, increasing fat burning, etc.). So I did some more digging and found that was exactly what bromocriptine was doing, mimicking leptin. So with that said, let's get to the topic of this book: bromocriptine, what it does, and how it works.

What is bromocriptine?

The effects of bromocriptine in the brain are complex and different sources give slightly different descriptions. To avoid utter confusion on the part of myself and the readers, I'm only going to focus on bromocriptine's primary mode of action, which is as a dopamine 2 (D2) receptor agonist (30). Bromocriptine is also a weak antagonist at the D1 receptor. Now that you're totally confused, let me explain what it means to

be a D2 receptor agonist or a weak D1 receptor antagonist.

I already told you that there are specific receptors in the body for the various hormones. There are other substances in the body, called neurotransmitters (the distinction between hormones and neurotransmitters is unimportant here) which also have specific receptors. Dopamine (DA) is one of the major neurotransmitters in the brain, along with serotonin and norepinephrine. There are many, many other minor neurotransmitters but those are the big three.

To keep it simple, and since it's the only one that concerns us, I'll only be focusing on DA here. Expectedly, there are specific DA receptors in various places in the body, especially in different parts of the brain. As with leptin, there are a number of different DA receptors, five in fact. We are only concerned with two of them in this booklet, the D1 and D2 receptors. So what does it mean to be a D1 antagonist or a D2 agonist?

An agonist is any drug or compound that stimulates a specific receptor. So, in the same way that a hormone/neurotransmitter will bind to the receptor and make 'stuff happen', an agonist drug does the same. So when an athlete takes the drug testosterone, which is technically an androgen receptor agonist, that drug binds to the receptor and makes stuff happen (in this case, increased muscle mass, etc.). The drug clenbuterol, and to a lesser degree ephedrine, work as beta-agonist drugs, meaning that they bind to beta-receptors and make 'stuff happen' (in this case, fat mobilization and burning, etc.). So a dopamine receptor agonist will bind a dopamine receptor and make stuff happen.

An antagonist is the opposite of an agonist. It is a drug that binds to a receptor without sending the normal metabolic signal. But it's more than just neutral. At the same time that it binds the receptor without sending a signal, it also prevents other compounds (such as DA itself) from binding. So a cortisol antagonist would bind to the cortisol receptor, without sending a metabolic signal, on top of preventing cortisol from binding.

As a D2 receptor agonist drug, bromocriptine will bind to the D2 receptor and cause an effect similar to if DA itself had bound. It also has weak antagonistic effect at the D1 receptor, which aren't that important in the big scheme of things. As a weak D1 antagonist, bromocriptine binds to the D1 receptor a little, preventing normal binding of DA a little. I won't really talk too much about this effect since it seems fairly unimportant in the big scheme of things.

Summing up: bromocriptine is a D2 receptor agonist which means that it binds to D2 receptors and activates them, just like DA itself would. It has weak antagonistic effects at the D1 receptor, which aren't that important so I won't spend any more time discussing them. It has a number of other complex actions at other receptors, but they aren't really that important to the topic of this booklet. So, for once, I'll avoid trying to confuse you with information overload.

What is bromocriptine used for?

Clinically, bromocriptine has been used primarily for three conditions: hyperprolactinemia, Parkinson's disease and acromegaly. Although none have much specific relevance to the topic of this book, I want to discuss them for the sake of completeness. I'll also come back to them when I talk about side-effects and risks, since there is a ton of data on bromocriptine's use for these conditions.

Hyperprolactinemia is a condition that sometimes occurs in women (and possibly obese men) and simply refers to an abnormal overproduction of the hormone prolactin. Prolactin is primarily involved in milk production after childbirth and the primary stimulus for prolactin's release is nipple stimulation. Prolactin also has effects on the immune system, and can affect overall hormone levels.

While normal prolactin levels aren't any big deal, hyperprolactinemia causes a number of problems including infertility and otherwise screwed up hormone levels. Considering that prolactin levels are going to be high when a woman is breast feeding, it makes a certain sense that the prolactin itself would render her infertile (it's not time to get pregnant when you're already breastfeeding one child).

It's when prolactin is abnormally elevated when she's not breast feeding (or in obese men) that high prolactin levels become a problem. It turns out that DA has an inhibitory effect on prolactin secretion in the brain, so women with low dopamine tend to overproduce and over secrete prolactin. Hence hyperprolactinemia.

At even low doses of 2.5-7.5 mg per day, bromocriptine (and other DA receptor agonists, most of which are very new) lowers prolactin levels significantly, which fixes most of the other problems. I should note now, and I'll come back to this, that bromocriptine does the same in animals: decreases prolactin levels significantly.

Parkinson's disease is a neurological disease that develops with aging in many individuals. In brief, there are neurons in your brain which produce DA, which

then trigger DA receptors. For a variety of reasons (i.e. stress, genetics), these neurons tend to die with age. Under certain circumstances, so many of these neurons die that the brain can no longer produce enough DA. This, along with some other defects leads to a variety of problems in Parkinson's patients. These include an inability to initiate movement, tremor, and other severe neurological defects. The movie 'Awakenings' with Robin Williams dealt with patients that had Parkinson's disease.

High dose bromocriptine (up to 40 mg per day) along with drugs such as L-dopa (a synthetic dopamine-like drug) and many others are used to deal with Parkinson's, in an attempt to restore normal functioning. Because of the severe pathology involved in Parkinson's, as well as the massive doses used, I don't consider most of the Parkinson's research to be really relevant for what I'm going to describe.

You can think of acromegaly as the disease that Andre "The Giant" had, since he's one of the most prominent folks who ever had it. Acromegaly occurs when the brain over-secretes growth hormone, leading to runaway growth of bone, muscle and connective tissue. It also causes death at a fairly young age. Bromocriptine normalizes GH release in these patients, but it takes massive doses, 100 mg per day or more. As with Parkinson's disease, the use of bromocriptine for the treatment of acromegaly really isn't that relevant for what I'm going to describe so I won't make much reference to this condition.

As I mentioned before, bromocriptine is an extremely old drug and was introduced nearly 30 years ago. The use of bromocriptine among athletes isn't new either. During the 80's, due primarily to the writings of Life Extensionists Pearson and Shaw, bromocriptine was often advocated as a growth hormone (GH) releaser. That alone may give it some benefits in terms of body recomposition, as GH is involved in fat burning and seems to help limit muscle loss while dieting.

As a quick tangent, which ties into my foreword, I consider the fact that bromocriptine has been around for so long as a benefit. I know that folks tend to think that new means better when it comes to this stuff but that's not always the case. With nearly 30 years of research behind it, we have an incredible amount of knowledge about what bromocriptine does, how it works and what the potential risks and side-effects are. To give you some idea, a search on Medline on bromocriptine, limiting the results to studies in human adults, turns up 2451 papers and studies. Even if we

assumed a mere 10 subjects per study, and most studies have more than that, that'd be 24,500 subjects studied over the last 30 years. Compared to most drugs, that's a ton.

As well, with nearly 30 years of clinical use, it's likely that literally millions of prescriptions have been written for bromocriptine. If there were major, horrible side-effects with short- or long-term use, we'd know about them by now. You can't usually say that about new drugs. I should mention right now, that like any drug you can care to name, bromocriptine has side effects that occur to one degree or another in most people. I'll discuss side-effects in great detail in Chapter 8 but I want to run through them quickly here.

Dizziness, low blood pressure, and nausea are the most commonly reported side effects and tend to occur with initial use or with an increase in dose. They typically go away in a day or two. Greater side effects including hallucinations and confusion occur at the higher doses used in severe diseases like Parkinson's and acromegaly (30). Like most drugs (even aspirin), bromocriptine has caused a handful of deaths over its 30 years of use but I'll address that later, too. At the doses I'm going to discuss, the side-effect and overall risk profile are minimal.

Additionally, and again in accordance with the foreword, the fact that bromocriptine is so old makes it easier to obtain than most newer drugs. It is prescription only in the US, but can be ordered from overseas without one, due to a loophole in the FDA guidelines. At the doses I'm going to describe (2.5-5 mg/day), bromocriptine is also cheap, approximately 50 cents to a dollar per day. So overall it meets my requirements as safe, effective, readily obtainable and affordable. I'll talk about some other potential drugs that can serve the same purpose as bromocriptine in a later chapter.

Bromocriptine and prolactin

I mentioned above that the primary use of bromocriptine is to lower prolactin levels in women. Again, levels of DA in the brain turn out to be controlling prolactin release (in addition to a number of other systems) and various dysfunctions, such as a tumor, can lead to women having low brain DA such that they overproduce prolactin. Bromocriptine fixes this like nobody's business, dropping prolactin levels like a rock.

Although prolactin isn't reduced to zero, it is moved towards the low-normal end of the range. It was this effect that prompted researchers to start studying bromocriptine so long ago. Knowing that bromocriptine lowered prolactin levels, they wanted to see what the effects of changing prolactin levels were.

Two researchers, Cincotta and Meier (you'll see their names a LOT in the reference list) appear to have done little else but study the effects of bromocriptine for the last 30 years. They've looked at a variety of different physiological parameters in everything from mice to hamsters to rats to pigs and finally to humans. I imagine they're a blast to party with, as long as you can talk intelligently about prolactin with them.

While their initial research focused almost obsessively on prolactin, their more recent research (as well as the work of some other researchers) is what got me to look at bromocriptine in a little more detail.

A few comments about prolactin

While the initial research by Cincotta, Meier and others focused primarily on changes in prolactin and the effects on body composition, they were barking up the wrong tree. It's true that prolactin is elevated in human obesity (31) and that causes a number of problems including autoimmune reactions and some other negative hormonal effects. Bromocriptine treatment fixes those too (32). But the changes in prolactin aren't the root cause of the changes in body composition, at least not in humans (and probably not in animals either).

As I said above, prolactin's main role in the body is to promote fat storage and milk production in breast tissue (and to inhibit female fertility while she's breast feeding). Outside of that, you don't find prolactin receptors on other types of fat cells, or in muscle. Prolactin itself doesn't affect human body composition, except inasmuch as it may affect other hormones such as testosterone or estrogen. As you'll soon see, bromocriptine has a number of metabolic effects that occur in addition to the lowering of prolactin. It's those other effects that are having the positive metabolic and body composition effects.

The point I'm making badly is that DA levels in the brain control a lot of different processes. One of those is prolactin levels, another is movement (related to

Parkinson's disease), another turns out to be metabolism. There are many others. But those effects aren't related outside of being controlled by the same neurotransmitter: DA. The relationship between dropping prolactin and other metabolic benefits is coincidental (or correlational if you prefer), not causal.

By activating the D2 receptors, bromocriptine causes a lot of stuff to happen, including lowering prolactin. In their early work, Cincotta and Meier confused the changes in prolactin with all of the other changes and assumed that the change in prolactin was causing it. As their later research showed, that simply isn't the case.

The reason I'm making this point is so that folks don't start looking for other ways to affect prolactin itself (coming soon, new Anti-Prolactin Fuel). To reiterate yet again, in humans, prolactin's main role is promoting the development of breast fat and milk production during pregnancy. It also affects immune function and has some behavioral effects such as promoting maternal behavior, which is a good thing if you've got a baby suckling at your breast. It also plays a role in sexual function and prevents women from becoming pregnant again while they are breast feeding (the old wives' tale about breast feeding being an excellent mode of birth control turns out to be correct). In terms of body composition, prolactin just isn't that big of a deal. It just happens that DA is controlling a metabolism AND controlling prolactin as well; the two aren't related.

Summary

Bromocriptine is a relatively old drug, that acts in the brain primarily as a dopamine-2 (D2) receptor agonist, meaning it activates the D2 receptor. It has weak antagonistic effects at the D1 receptor and a variety of other complex effects that aren't really that important to this booklet.

Clinically, bromocriptine has been used to treat excessive prolactin secretion, Parkinson's disease, and acromegaly. Doses run from 2.5-7.5 mg/day for hyperprolactinemia to 40 mg/day for Parkinson's to 100 mg/day for acromegaly, respectively.

It has also been used previously by bodybuilders and athletes as a growth hormone (GH) releaser. Side effects at low doses are minor and transient, but they get worse at higher doses (as with most drugs). Although the initially studied effect of

bromocriptine focused obsessively on the changes in prolactin levels, it turns out that the metabolic and body composition effects we are interested in are not caused by changes in prolactin levels. The relationship between changing prolactin and changing everything else (metabolism, body composition, etc.) was simply coincidental. So now, let's look at what those metabolic and other effects actually are. Then I'll tell you how bromocriptine actually works.

Chapter 5: What bromocriptine does

Now that you know what bromocriptine is, let's look at what it does in both animals and humans. As we go through the research, I'll be making comments that help to tie bromocriptine in with the information I presented on leptin in previous chapters.

First I want to present the body composition data, followed by a short tangent, and then I'll present the other metabolic effects of bromocriptine in both animals and humans. Then I can finally tell you how bromocriptine actually works in Chapter 6.

Effects in animals: bodyfat changes

I already mentioned that bromocriptine lowers prolactin levels in animals, but so what? In examining the effects of bromocriptine on prolactin levels in animals, researchers observed another effect as well: when bromocriptine was administered at the correct time of day, the animals lost a significant amount of bodyfat. Fat loss, now we're getting somewhere.

To give you some representative numbers: hamsters and mice reduce their bodyfat by at least 50% within 10-15 days of bromocriptine being given to them. That's right, bodyfat is cut in half in ~2 weeks. In rats, a 29% reduction in bodyfat in 8 weeks was seen. I want to make sure and point out that, because of their overall shorter life spans, animals respond to nearly everything much faster than humans. Even rats, who have a longer lifespan than mice, take longer to see results and they're smaller overall (compare 29% reduction in bodyfat in 8 weeks to a 50% reduction in 2 weeks). On average, humans take at least three times as long to respond as mice or rats.

In addition, total cholesterol was reduced by 17% in hamsters, 41% in mice, and 30% in rats given bromocriptine, suggesting an overall change in lipid (fat) metabolism in these animals. It didn't appear to matter whether the bromocriptine was given orally, via injection, or via time release implants; the same results were observed (37).

But that's not all. In these same animal models, as bodyfat was dropping, bodyweight was either staying the same or dropping much more slowly. This means

that the animals were at least maintaining, or in some cases gaining muscle mass. For example, in pigs, implantation of a bromocriptine-releasing pellet for 30 days decreased bodyfat significantly while increasing muscle mass (38). By whatever mechanism, bromocriptine was not only generating fat loss, it was causing protein retention in these animal's bodies.

So, in animals at least, bromocriptine caused fat loss with simultaneous muscle gain, sort of like clenbuterol (a beta-agonist drug which causes significant fat loss and muscle gain in animals). Since clenbuterol didn't exist at that time, Cincotta and Meier likened the effects of bromocriptine to that of growth hormone (GH) which was the only hormone that had really been shown to have those kinds of effects at that time. Considering the known effect of bromocriptine on GH release, this seemed logical. They were ultimately wrong, mind you, but based on the science of the day, it made sense.

Effects in humans: bodyfat

Ok, so what? There's lots of stuff that does amazing things in animals that doesn't do jack squat in humans. And anybody who's read my writings on the internet knows I'm usually the first to criticize the use of animal models, unless that model has been shown to be a good one for humans. We aren't rats, mice, hamsters or pigs (some women may disagree with that last one, in terms of how men act) so research data on those animals can't automatically be extrapolated to humans.

So what about human data, is there any supporting bromocriptine's effects on body composition? The answer is that, while it's limited, the data does exist and the mechanisms appear to be the same as in the animal models. And as we move forward into the next chapter, and I explain the mechanism by which bromocriptine works, you'll see why the data applies to everybody from animals to obese dieters to lean individuals .

In the earliest study, bromocriptine was given at either 1.25 or 2.5 mg/day to obese post-menopausal women and bodyfat was monitored by skinfold (4 site: iliac, triceps, biceps, and subscapular) and bodyweight (39). Diet was not controlled but the subjects were told not to change anything.

The results were excellent, to say the least. In six weeks, the average drop in

bodyfat percentage in the women was from 37.3% to 33.8%. Skinfold measurements (in millimeters) dropped by 25%. This change ultimately represented a loss of 8.6 pounds of fat in 6 weeks, roughly 1.5 lbs fat/week, with no change in diet. In two subjects who were kept on bromocriptine for 20 weeks, the reduction in total skinfolds was nearly doubled, to a 45% reduction. If a 25% reduction in skinfolds equaled 8.6 pounds of fat, 45% would be almost twice that, nearly 16 pounds of fat lost in 20 weeks with no change in diet. Again, the women lost nearly one and a half pounds of fat per week with no change in diet, just adding low-dose daily bromocriptine.

In a follow up part of the same study, Type II diabetic women were given bromocriptine for 4-8 weeks to look at the effects on bodyfat and blood glucose concentrations (39). One half of the women were on hypoglycemic/diabetic drugs, the other half on injectable insulin. While the results weren't as great as in the post-menopausal women, the groups still reduced bodyfat by 10 lbs in the hypoglycemic drug group and 3 lbs in the insulin group. Again, that was over 4-8 weeks of the study.

The second part of the study actually demonstrates two things. The first is that bromocriptine causes fat loss without a change in anything else (diet or exercise), at least in post-menopausal women. The second is that injectable insulin pretty much shuts fat loss down cold. Considering how potent insulin is at stopping fat mobilization, it's a surprise that the subjects on insulin lost any fat at all.

I should note that post-menopausal women aren't really a good model of anything except other post-menopausal women so don't get too excited just yet (unless you're a post-menopausal woman). The massive hormonal changes, including a complete cessation of estrogen and progesterone production, lead to an enormous number of metabolic changes, most of which are negative. Those changes alone probably explain the profound results that were seen in the previous study: considering the extreme hormonal situation, post-menopausal women may be a population that just get tons out of the drug. But it has literally no relevance to any other group.

In the next study, obese men and women (obesity was defined as >25% bodyfat for men, >30% bodyfat for women) combined a calorie restricted diet (70% of maintenance calories) with 1.6-2.4 mg of bromocriptine per day for 18 weeks and both bodyweight and bodyfat were measured (40). They were compared to a control group that received an inert placebo.

At the end of 18 weeks, the bromocriptine group had lost an average of 6.3 kg

(14 lbs) of weight, of which 5.4 kg (12 lbs) of fat. So only 2 lbs of lean body mass was lost. The placebo group lost a paltry 0.9 kg (2 lbs) of weight and 1.5 kg (3.3 lbs) of fat. Clearly, these results aren't nearly as great as in the post-menopausal women. In fact, the bromocriptine group didn't even really lose more fat than you'd expect from diet alone: 14 pounds of fat lost in 18 weeks is about 1.2 lbs fat/week, about what you'd expect from a decent diet in the first place.

Actually, that's not entirely true, most diets tend to cause a fairly large loss of lean body mass, approaching one-half of the total weight loss. At the very least, bromocriptine appeared to have a protein-sparing effect, which would be benefit enough.

Even with that major advantage, perhaps, the more interesting observation is the difference between the bromocriptine group and the placebo group. That is, even if the bromocriptine group didn't lose more weight than you'd expect from the diet alone, why did they do so much better than the placebo group?

The answer is that the placebo group lost weight/fat for the first 6 weeks of the study and then started gaining it back for the remainder of the study, while the bromocriptine group lost weight/fat consistently throughout the study. The researchers think that the placebo group quit following the diet because of hunger which is a common cause of diet failure. Now, hunger while dieting ties in with what I talked about in the leptin chapters, as it is one of the most common responses of the brain to dropping leptin. And although it wasn't measured, it wouldn't surprise me to find out that the bromocriptine group (for reasons that will make sense in the next chapter) also avoided the normal metabolic slowdown that occurs with dieting.

This also ties in with the study I mentioned in the addendum to Chapter 3, where bringing leptin back to pre-diet levels corrected some of the metabolic effects of dieting. Assuming that bromocriptine is mimicking leptin somehow, we would expect that the use of bromocriptine during a diet would prevent some, if not all, of the normal adaptations to dieting. This would keep the diet working longer and more effectively, even if no other effects occurred.

I should also mention that, in this study, there was also a significant increase in glucose tolerance and insulin sensitivity in the bromocriptine group. Since insulin resistance tends to occur with age, as well as with obesity, this would be an additional benefit. I'll discuss the non-fat loss metabolic effects a little further below.

Insulin, insulin resistance and diabetes

To understand the next batch of data, I have to make a quick tangent and give you a very rough overview of insulin resistance, what it is and what it causes to happen in the body. Please realize that this is a topic on which endless chapters could be written, but I'm going to spare you the details and just sketch out the basics. Maybe I'll write the Insulin Resistance Handbook some day; for now you only get the short course.

Insulin is a peptide (protein) based hormone that is released from the pancreas primarily in response to changes in blood glucose levels. Although insulin has numerous effects in the human body, its primary role is in the maintenance of proper blood glucose levels. Although there are occasional exceptions, generally insulin goes up as blood glucose goes up, and down as it goes down.

As insulin goes up (in response to increasing blood glucose levels), it tries to bring blood glucose back down by pushing glucose into muscle and fat cells; as insulin goes down (in response to decreasing blood glucose levels), it allows blood glucose to come back up again. Kind of like a thermostat, insulin acts as a very basic feedback loop (although I should mention that other hormones are also involved in blood glucose regulation as well) to try to keep blood glucose levels within 'normal' ranges.

Along with its primary role of regulating blood glucose, insulin also acts as a general storage hormone in the body, shifting the body from a state of nutrient mobilization (pulling calories out of cells for use) to one of nutrient storage (putting calories into cells to be used later or using them right then and there). So when you eat a meal, insulin levels will go up depending on a host of factors including the amounts of each nutrient (protein, carbohydrates, fat, fiber), the form of the meal (liquid or solid), and the types of each nutrient in the meal.

As with other hormones, when insulin levels go up, that insulin floats around until it runs into an insulin receptor where it binds and causes stuff to happen. What happens depends on what tissue you're talking about (41). In the liver, insulin promotes liver glycogen storage, increases protein synthesis, and increases fat storage. In the muscle, its effects are similar: insulin increases glucose uptake and glycogen storage, increases protein synthesis, and increases the storage of fat as intramuscular triglycerides. In fat cells, insulin acts to increase glucose uptake and to

increase both fat synthesis and storage.

Now, knowing that insulin's main role is to move nutrients out of the bloodstream and into liver, muscle or fat cells, let's think about what happens when those cells become resistant to the effects of insulin. That is, if insulin's main job is to move nutrients out of the bloodstream, and insulin resistance prevents it from doing its main job, what happens? If you guessed that nutrients would accumulate in the bloodstream, you guessed right.

Since blood glucose can't be cleared effectively, due to insulin resistance, blood glucose levels rise and the person develops hyperglycemia (above normal blood glucose). Since the body is still trying to bring blood glucose back down, it continues to release more and more insulin (which can eventually cause the pancreas to shut down completely) causing hyperinsulinemia (above normal insulin levels).

Since fat can't be moved out of the bloodstream either, the person develops hyperlipidemia or hypertriglyceridemia (depending on which technical sounding word you prefer, both mean above normal fat levels in the bloodstream). Because of other changes, mainly in liver metabolism, folks who are insulin resistant also have above normal cholesterol levels, called hypercholesterolemia. There are myriad other effects that occur in insulin resistance as well, but this should be sufficient to give you a basic idea of what's going on. To put it as bluntly as possible, insulin resistance is pretty much one big metabolic clusterfuck.

One final effect I want to mention is that severe insulin resistance causes a negative partitioning of calories away from muscle cells and towards fat cells. The basic cause is that muscle cells become insulin resistant before fat cells under most circumstances. That is, typically muscle cells become insulin resistant first, causing calories to be shuttled more rapidly into fat cells. Eventually the fat cells become insulin resistant too, and the effects described above (an accumulation of nutrients in the bloodstream) occurs.

Without going into too much detail, just realize that being able to drive nutrients (glucose and amino acids) into muscle tissue is critical to maintaining normal muscle growth and function. If insulin can't do its job, because of insulin resistance in the muscle cell, muscle will essentially 'starve' and shrink. At the same time, since calories can't be stored in muscle cells, they get put into fat cells instead (at least until the fat cells become insulin resistant as well).

The take home message is that insulin resistance in the muscle, which is where it typically occurs first, causes a negative partitioning effect, causing muscle loss and fat gain, even with no real change in caloric intake. I should note that this same phenomenon occurs in other conditions such as cancer wasting, which just happen to induce severe insulin resistance.

The other take home message is that reversing of fixing insulin resistance, through whatever means would tend to reverse all of the above described effects. Fat loss would occur, frequently with a simultaneous gain in muscle mass, and blood levels of glucose, insulin, triglycerides, and cholesterol would go down. Keep that in mind as I discuss the other effects of bromocriptine below.

I should also mention that insulin resistance and one type of diabetes, called Type II diabetes, are inter-related. So don't get freaked when I move from talking about insulin resistance to diabetes in the next section. Insulin resistance (also called the Insulin Resistance Syndrome, the Metabolic Syndrome, or Syndrome X) is essentially a pre-diabetic state. Left unchecked, insulin resistance will develop into full blown Type II diabetes.

Now, there are many different factors which determine the degree of insulin resistance. Genetics play a key role, of course, as does total calorie intake, type of food intake, and activity levels. A high-calorie, high-carbohydrate (especially refined carbohydrates), high-fat diet coupled with low levels of activity causes muscle and fat cells (again, muscle cells before fat cells in general) to become insulin resistant through a variety of mechanisms. Some of these mechanisms are purely local, that is occurring from changes directly in the muscle or fat cells but I don't want to get too far into the details.

As it turns out, the brain is also playing a controlling hand in inducing insulin resistance and calorie partitioning by controlling hormone and neurotransmitter levels (remember from an earlier chapter that the brain is not only getting signals from the rest of the body, but sending signals back out).

So that's the overview of insulin resistance/Type II diabetes, what it is and what it causes to happen in the body. Now let's reconnect that information with bromocriptine with a short segue.

The segue: Obese Syrian Hamsters

Remember from an earlier chapter that, while the body is sending signals to the brain, the brain is sending signals back to the periphery via changes in hormone levels. In addition to all of the local effects that induce insulin resistance, it turns out that the brain is also playing a role in causing insulin resistance. No real surprise, honestly. It'd be more surprising if it didn't work that way.

In non-tropical animals, for example, it's not uncommon to see shifts in whole body metabolism and insulin resistance at different times of the year. This causes the animals to change body composition significantly without any change in total food intake. The partitioning of calories changes because of changes in the animal's overall physiology, controlled by the brain.

I mention non-tropical animals specifically because it is those animals that had to contend with annual changes in food availability (similar to most humans). In tropical climates, food is available year round, explaining why tropical animals (and probably humans who's ethnic background is tropically based) don't become obese readily: they developed different genetics, since they never had to contend with seasonal food availability.

In any event, during one shift, animals become insulin resistant in muscle cells which serves to preferentially partition calories into fat cells. This causes them to lose muscle mass and become obese, so that they are better equipped to survive starvation. During the reverse shift, the opposite occurs: muscle insulin sensitivity goes back up, the body pulls calories back out of fat cells, and muscle mass increases. This causes these animals to lose the excess bodyfat and regain their lost muscle mass, to better survive now that food is available.

That is, the non-tropical animals, who evolved under the same seasonal food availability that we did, show adaptive changes that help to promote survival, just as we do. The most common pattern, and the one that we evolved on as well, was to become insulin resistant and obese during certain parts of the year, in order to survive those periods when food isn't available (42). And this change turns out to be mediated mainly by changes in the brain.

One of the more well studied animals, and one of the most interesting, is the seasonally obese Syrian hamster. As described above, and as its name suggests, this hamster becomes obese at certain times of the year and the effects appears to

be mediated by changes in brain chemistry. Mainly it appears that the brain of the Syrian hamster changes its sensitivity to leptin depending on the time of the year, and this causes the insulin resistance seen. Along with this change comes the other aspects of obesity: blood glucose defects, hyperglycemia, hypertriglyceridemia, calorie partitioning into fat cells, and everything else associated with insulin resistance. It's all adaptive to help the little critter survive better. So it gets obese at certain times of the year, and lean at others, and these shifts are being controlled by its brain.

These changes are being mediated primarily by changes in light levels. These changes alter melatonin levels, which appears to be controlling the brain's sensitivity to leptin (42). Researchers can actually change the overall metabolism of the Syrian hamster by subjecting them to different light levels and durations. If you put the hamsters in a situation that mimics light levels during one part of the year, you will see the same shifts as occur under 'normal' lighting conditions for that time of the year. That is, if you mimic one set of light levels, you get insulin resistance and obesity; if you mimic the reverse, you get insulin sensitivity and leanness.

As it turns out, changing sensitivity to leptin in the brain causes characteristic changes to occur in levels of various brain chemicals, including prolactin (which is why Cincotta and Meier originally noticed it). You also see characteristic changes in other hormones in the animal's body, including increased cortisol, which significantly affects tissue insulin sensitivity. When researchers give these animals bromocriptine at the right times of the day it prevents the normal obesity that would occur (43). Essentially, by 'tricking' the hamster's brain into thinking it's a different time of the year, it doesn't become insulin resistant and become obese. Alternately, if you give bromocriptine at the 'wrong' time of the day, you make the animal obese and insulin resistant.

Later studies have shown that bromocriptine dosing, again at the right time of day, also corrects some of the changes in neurochemistry (in the hypothalamus) which are causing the insulin resistant/obese syndrome (42,47). The researchers have suggested that properly timed bromocriptine dosing actually 'redirects' their metabolism to one of lean animals (46). Now, if this doesn't sound like some of the information on leptin I've presented, you really haven't been paying attention. The ultimate point is that, whatever mechanisms are involved, bromocriptine is working at the brain to correct a lot of deficits elsewhere in the body, deficits similar to the ones

seen with low leptin or leptin resistance. This includes not only metabolic defects involved in metabolism and fat burning, but also those involved in the insulin resistance syndrome, diabetes, and calorie partitioning.

While humans don't appear to be as sensitive to changing amounts of light, there is evidence that some of the same biological mechanisms are still operating (42,47). It may be that we lost those adaptations somewhere during our evolution or we simply don't observe it to as great a degree in our modern environment. Under most circumstances, humans don't go through the major parts of the annual light/dark cycles, because of our reliance on artificial lighting. I suspect that the same biology is present in humans, but we don't really see it because of the changes in our environment.

Now, so far I haven't really presented much to support the idea that what's going on in the Syrian hamster is operating in humans. It would make sense, mind you, based on our evolutionary past, but the data just really isn't there, not in terms of research on the brain. And while people typically get fatter in the winter, and leaner in the summer, it's hard to distinguish changes in our physiology from changes in our behavior. During the winter, most people eat more and tend to be less active, which we would expect to cause fat gain; during the summer, we want to look better in a bathing suit and get back in the gym and start eating more healthily. You can't conclude it's all from changes in physiology, because behavior patterns can be just as (or more) important.

This is all sort of tangential to the point of this section anyhow. The point I really want to make here is that there are characteristic alterations in brain chemistry that are involved in changes insulin sensitivity/resistance as well as the metabolic consequences of those changes. The Syrian hamster goes through those changes seasonally, making it relatively easy to study. If you recall the data on both the OB and DB mice, these same changes in overall physiology also are associated with low/no leptin levels (OB mouse), or leptin resistance (DB mouse). In all three models, correcting the neurobiological defects (in this case, with bromocriptine) fixes the other problems as well.

So, with that said, let's look at the rest of the metabolic effects of bromocriptine.

Effects on animals: other metabolic effects

In addition to its effects on bodyfat levels, researchers have examined other metabolic effects of bromocriptine in animal models. I already mentioned one or two of these effects above, mentioning bromocriptine lowers both total cholesterol and triglyceride levels in most animal models (33). That observation alone, a change in both cholesterol and triglyceride levels, suggests an overall change in the animal's fat metabolism. Liver metabolism of cholesterol, as well as changes in liver production of triglycerides (or the body's utilization or both) would both explain these results. These changes would also be consistent with improvements in insulin sensitivity for complex reasons that aren't that important for this booklet.

However, the early research isn't quite as exciting as some of the more recent stuff. I already bored you to death with the different animal models of obesity and I'm going to be referring back to one of them in this section: the OB mouse. To refresh your memory, OB mice produce no leptin and their brains basically always think that they're starving to death. Because of this, the OB mouse show a significantly decreased metabolic rate and fat burning, as well as severe hunger and increased bodyfat deposition.

Similar to the DB (diabetic) mice, the OB mice also have super high insulin, blood glucose, blood free fatty acid, blood cholesterol, and blood triglyceride levels. Like the DB mouse, they are insulin resistant. To reiterate, the OB mouse isn't really a good example of human obesity, since only one or two humans have been found who lack leptin completely. However, recall that the effects of no leptin are at least similar to what happens in the case of either low leptin (due to low bodyfat levels and dieting) or leptin resistance. In all cases, the brain receives a diminished leptin signal. So studies of the OB mouse can be informative.

As it turns out bromocriptine (combined with a D1 receptor agonist which simply has the chemical name of SKF38393) has profoundly beneficial effects on the OB mice. Administration of either bromocriptine or SKF38393 singularly helps to correct all of the metabolic defects listed above, while administration of both at the same time has an even greater effect. Let's look at some numbers.

In one study, OB mice were given bromocriptine, SKF38393 or both (37). In the combined group, there was a reduction in bodyweight, bodyfat percentage (down 40%), food consumption (down 42%), blood glucose (down 59%), triglyceride levels

(down 37%), free fatty acid levels (down 45%), and insulin levels (down 49%). Body protein (i.e. lean body mass) went up by 8%. This all occurred in 2 weeks and is exactly what you'd expect from a drug that was correcting metabolism and/or the root cause of Type II diabetes. Again, let me point out that two weeks for a mouse is a longer period in humans.

In another study, the same OB mice were given two weeks of bromocriptine and SKF treatment (38). Food consumption decreased by 55%, oxygen uptake (metabolic rate) increased 2.4 times over normal (noting that it is normally very low in these mice and the 2.4 times increase merely brought them back to normal), and the respiratory quotient (a measure of fuel use) decreased significantly indicating increased fat burning. Blood glucose and blood free fatty acid levels were also decreased. This could represent either a reduction in glucose or free fatty acid production, an increased ability to utilize glucose or free fatty acids, or some combination of the two. When the OB mice who were given bromocriptine/SKF38393 were compared to normal lean mice, they were found to be basically identical. That is, bromocriptine/SKF38393 normalized the metabolic defects that are causing the problems in the OB mice, namely no leptin. Put differently, the combination treatment corrected all of the metabolic defects caused by a complete lack of leptin in the OB mice.

Ok, now we're really getting somewhere and maybe you're starting to see how bromocriptine ties in with the entire leptin issue from the past chapters. Recalling from those chapters, note that both dropping leptin levels (with dieting) and/or leptin resistance lead to a fairly characteristic metabolic pattern: depressed metabolic rate, depressed fat burning, increased appetite, and an increased tendency for fat storage. The OB mice, who make no leptin at all, are an extreme example of this but the point should be pretty clear: however it's working, bromocriptine is 'mimicking' the effects of leptin. It's correcting metabolism in a lot of ways, ranging from metabolic rate and fat burning, to most of the defects seen in Type II diabetes. The question that's still unresolved is how it's doing its magic. Slowly I'm getting there.

Bromocriptine effects on humans: other effects

Before I tie everything together, I want to describe some of the other metabolic effects of bromocriptine in humans. That is, in addition to effects on bodyfat and

bodyweight levels, and the aforementioned effects on prolactin levels, low-dose bromocriptine also has other effects on humans metabolically. They are quite similar to some of the effects seen in the OB mouse. They are all also related to the information in insulin resistance I presented above.

In one study, a slightly modified form of bromocriptine called Ergoset (tm) was given to obese, nondiabetic, hyperinsulinemic women. Starting at 0.8 mg/day (to minimize side effects) and building up to a maximum of 4.8 mg/day over 6 weeks, these women were monitored for changes in blood glucose, blood free fatty acid, triglyceride, and cholesterol levels (39). On top of the reduction in prolactin, there was a significant decrease in 24 hour levels of all variables measured. Bromocriptine corrected all of the major defects seen in Type II diabetes. The researchers concluded that '...Ergoset could be of therapeutic benefit in clinical conditions of hyperglycemia and/or dyslipidemia.' Which is just a techie way of saying that it might help folks with high blood glucose and high blood triglyceride levels, both of which tend to occur with both obesity and diabetes.

I want to mention that researchers made sure that the women didn't lose weight by setting their diet at maintenance levels (39). This was to separate out the effects of the bromocriptine from weight loss itself (which is known to improve blood glucose and triglyceride levels). Whether or not fat was lost is impossible to know as bodyfat percentage was not measured. On top of the major metabolic improvements seen, one point I want to make about this study is that it demonstrates that bromocriptine doesn't appear to cause weight or fat loss without caloric restriction or exercise (again, post-menopausal women excepted). What this means is that for people who are suffering from diabetes, and want to help correct some of the metabolic defects, bromocriptine use may be beneficial, even if weight/fat loss is not the explicit goal. That is, bromocriptine by itself, without any weight or fat loss appears to improve health indices in diabetic individuals.

In a more recent study, the same protocol was followed (i.e. 0.8 mg/day of bromocriptine increasing to 4.8 mg/day over 6 weeks) in 22 obese subjects with Type II diabetes for 18 weeks (40). Similar to the first study, while there were no significant changes in fat or weight (diet was set at maintenance levels and body composition was measured in this study), there were significant improvements in blood glucose, HbA1c (glycosylated hemoglobin, a marker of diabetic complications), as well as increased sensitivity to insulin. It was estimated that these changes amounted to

roughly a 35-37% reduction in overall diabetic risk in these patients over time.

Basically, the bromocriptine helped to correct many of the metabolic problems seen in Type II diabetes, many of which also occur in the OB mouse described in the last section (40). As with the first study, these changes occurred in the absence of any real changes in weight or bodyfat percentage. Once again, this study indicates that bromocriptine by itself does not cause fat loss in the absence of caloric restriction (or exercise).

I should also mention another recent study which found no effect of bromocriptine in diabetics (48). However, they did a few things differently than all of the studies to date, including giving the bromocriptine at night (instead of in the morning, and it does appear to matter) and measuring improvements in blood glucose differently than in the other studies (49).

For completeness, I want to mention a few of the other metabolic effects which were observed in these populations and studies (note: this data comes from the FDA docket discussed in detail in the appendix). One of the first was a reduction in overall rates of lipolysis (fat mobilization). Now, before everyone gets their panties in a twist, lemme explain that this isn't negative in this case. Because of their insulin resistance, on top of ramped up sympathetic nervous system tone, obese individuals have an extremely overactive lipolytic response; they release free fatty acids (FFAs) into the bloodstream at extremely above normal levels.

While this sounds wonderful to the dieting mentality, it's not. Quite in fact, many of the metabolic defects (including insulin resistance and overactive glucose production in the liver) seen in Type II diabetes are related to the over-release of FFAs into the bloodstream. By helping to normalize insulin sensitivity, as well as decreasing an overactive sympathetic nervous system, bromocriptine brings blood FFAs back to normal. This doesn't mean that it will make normal lipolysis more difficult; it simply normalizes a defect. In fact, as you'll understand after the next chapter, bromocriptine should help to keep FFA mobilization higher in lean individuals who are dieting. But I'm getting ahead of myself.

On a related note, another noted effect of bromocriptine in obese individuals is a normalization of growth hormone (GH) release, which is typically blunted in obesity. For a variety of reasons, most likely the hyperglycemia and hyperinsulinemia that occurs because of insulin resistance, obese individuals show a blunted GH response during sleeping hours. This response is thought to be part of overall

'normal' physiology and may be one of many contributors to the overall metabolic problems seen. Bromocriptine, by helping to lower blood glucose and insulin, and by correcting the central (brain) defects, normalizes the bedtime GH response in obese individuals. In a similar vein, although bromocriptine did not affect levels of thyroid hormones per se, levels of Thyroid Stimulating Hormone (TSH), which are frequently affected in obesity, were normalized.

In conclusion, the small amount of research available suggests that bromocriptine helps to 'fix' some of the metabolic defects in diabetic individuals, on top of its effects on fat loss. As with experimental animals, it normalizes a number of metabolic parameters towards those of lean, otherwise 'normal' individuals.

Summary

Without even knowing the exact mechanisms involved, you can see that bromocriptine does some pretty profound things metabolically speaking. In animal models, it reduces bodyfat significantly very quickly. In humans, it has the greatest effect in post-menopausal women, but also improves fat loss in obese individuals on a diet, primarily by keeping the diet working longer and more effectively. As noted, except in post-menopausal women, bromocriptine does not cause fat loss without caloric restriction (or exercise).

In addition to the fat loss effects, bromocriptine appears to normalize the metabolic defects seen in both obese humans and the OB mouse which are related to insulin resistance and Type II diabetes. High insulin levels, high blood glucose, high blood free fatty acid concentrations, high blood cholesterol, increased fat gain with muscle loss, low metabolic rate, hunger and all the rest are corrected with bromocriptine administration due to changes in brain chemistry. And while, bromocriptine works best when it's coupled with a specific D1 receptor agonist (a chemical called SKF38393), it works by itself too.

In any case, bromocriptine appears to be 'fixing' whatever metabolic defect is occurring in human obesity and the OB mice. Since very lean humans and/or dieting humans can have extremely low leptin levels, the OB mouse is an approximate (albeit extreme) representation. And I've already explained how leptin resistance can mimic the effects of low leptin; in both cases, a lower leptin 'signal' is received by the brain.

Now, you know what bromocriptine is and what it does. Let's see how it works.

Chapter 6: How bromocriptine works

The previous chapters pretty much explain the line of thought I followed that got me interested in bromocriptine in the first place, how I put the puzzle together from both ends so to speak. The leptin research was explaining the left hand part of the puzzle, how the system is supposed to work. The animal and human data showed where the system could go wrong when leptin got too low, or when the signal wasn't being sent very well. The bromocriptine data demonstrated how it could be fixed without leptin itself. That left one final piece to link them: the mechanism. That is, how does bromocriptine actually work?

A few years ago, I would have had to guess, and probably would have guessed wrong. Thankfully, research into brain chemistry has advanced to the point that we can find out what's going on, at least to some degree. Remember the graphic a few chapters back explaining how hormones work? So far I've discussed every part of it except for one part. In this chapter, it's time to talk about the arrow between the 'receptor' and 'stuff happens' step: that is how binding of leptin to its receptor causes the stuff to happen.

A tale of two more hormones: NPY and CRH

As research into the neurochemistry of appetite and bodyweight regulation took off, it quickly became clear that the system was extremely complex. Although leptin was the main signal from bodyfat to the brain, there were literally a dozen (or more) other chemicals that were affecting metabolism, hormones, appetite, etc. further downstream. These got divided up into orexins, which stimulate appetite, and anorexins, which blunt it. They all have horribly complex names, such as pro-opiomelanocortin (POMC), alpha-melanocyte stimulating hormone (alpha-MSH), cocaine and amphetamine regulated transcript (CART) and many others (41). More are still being found.

However, we only need concern ourselves with the two that appear to be the primary compounds involved in 'sending' the signal from leptin. These two

compounds are neuropeptide Y (NPY) and corticotropin-releasing hormone (CRH). Both cause a number of effects in the body, including the regulation of appetite, hormone release, and metabolic rate. NPY also appears to turn attention towards food. If you inject NPY into the brain of a rat, it will forego sex in order to drink sugar water. Basically, when NPY is high, everything takes a back seat to food (50). I mentioned very early in this book that injecting insulin into animals blunts their hunger, and it turns out that it does this by decreasing NPY levels (8). If you inject leptin into their brains (or into the DB mouse), the same thing happens: NPY and CRH normalize and so does metabolism.

In addition, NPY and CRH appear to be intimately involved in nutrient partitioning, where calories go after you ingest them (51). When leptin is high, changes in NPY and CRH decrease fat storage and at least try to promote leanness. There is also decrease in cortisol levels (from normalization of CRH) which is part of the improvement in insulin resistance. As I mentioned, leptin doesn't work tremendously well in humans to promote leanness, having its major effect in telling your body to adapt during starvation.

As leptin drops, or you get a decreased leptin signal from leptin resistance, you see a characteristic change in both NPY and CRH and an increased tendency towards fat storage, due to changes in metabolic rate, fat burning, etc. You also get insulin resistance (remember the Obese Syrian Hamster?). Summarizing, NPY and CRH are the main link between leptin and the end results that are seen in terms of metabolic rate, fat burning, hormones, appetite, etc. (41). Leptin (and insulin, and as it turns out, ghrelin) is affecting NPY and CRH, and that's affecting metabolism further downstream.

Which brings us, finally, to the last piece of the puzzle. Researchers gave the same cocktail of bromocriptine (a D2 agonist) and SKF38393 (a D1 agonist) to the same OB mice used in the other studies, and directly measured levels of NPY and CRH by sticking a needle in their little rat brains. Activating the dopamine (DA) receptors lowers levels of NPY and CRH just like leptin would (52). This makes the mouse brain think everything is normal, and the rest of the metabolic picture corrects.

Depending on what part of the brain the researchers looked at, NPY dropped by 39-43%; with a 45-50% decrease in CRH. This brought levels back down to those seen in normal mice (52). Bromocriptine and SKF38393, through their effect at the DA receptors, normalized brain chemistry. This suggests strongly that brain DA levels

and their activation of the DA receptors is controlling metabolism further on, by affecting NPY and CRH levels.

As a further data point in this regard, a class of drugs called 'atypical antipsychotic' drugs has long been known to cause severe weight gain and problems with blood glucose and lipid levels, both of which are involved in insulin resistance syndrome (53). While some of this is due to increased appetite, there are other effects such as decreased metabolic rate. It turns out that part of the way that these drugs work is by blocking the D2 receptor (54). Block the DA receptor, and the brain thinks its starving, and adapts accordingly.

And, as the final nail in this coffin, new research has shown up implicating problems with both DA levels and the DA receptor as being involved in obesity (43, 44). Simply put, DA levels and activation of DA receptors is controlling a major part of metabolism, obesity, etc. You can expect the development of new DA agonist drugs for obesity to start showing up within a few years. For now, you have a head start, a 30 year-old drug called bromocriptine.

But that still leaves one last question: does leptin work via DA?

And finally, the punch line

You've waded through a lot of information to get here, and probably know more about the neurobiology of bodyweight regulation than most people out there. I hope it was worth it. Before I finish up, lemme sum up briefly.

We know that low leptin (or leptin resistance) leads to changes in NPY and CRH which negatively affects metabolism. We know that bromocriptine (or bromocriptine plus another drug) activates the D2 (and D1) receptor and normalizes levels of NPY and CRH (and thus metabolism). So we ask the logical question: does leptin work by changing brain DA levels?

The answer, as you might have guessed (or I wouldn't have written this book) is yes. As it turns out, a group of neurons in the hypothalamus (the area of the brain which plays a key role in controlling hunger) which produce DA in the brain have leptin receptors (57). This suggests that binding of leptin to those neurons is affecting DA levels.

Perhaps more conclusively, a recent study has measured both leptin and DA

levels in humans who were dieting. As leptin dropped in response to the diet, levels of DA dropped as well (58) supporting the existence of a causal link between the two; cortisol levels increased as well, which makes sense considering the effects of leptin on CRH. As leptin drops, so do brain DA levels causing NPY/CRH levels to become abnormal which screws up metabolism; as leptin goes up so do brain DA levels (assuming no leptin resistance) causing NPY/CRH to normalize and fix metabolism.

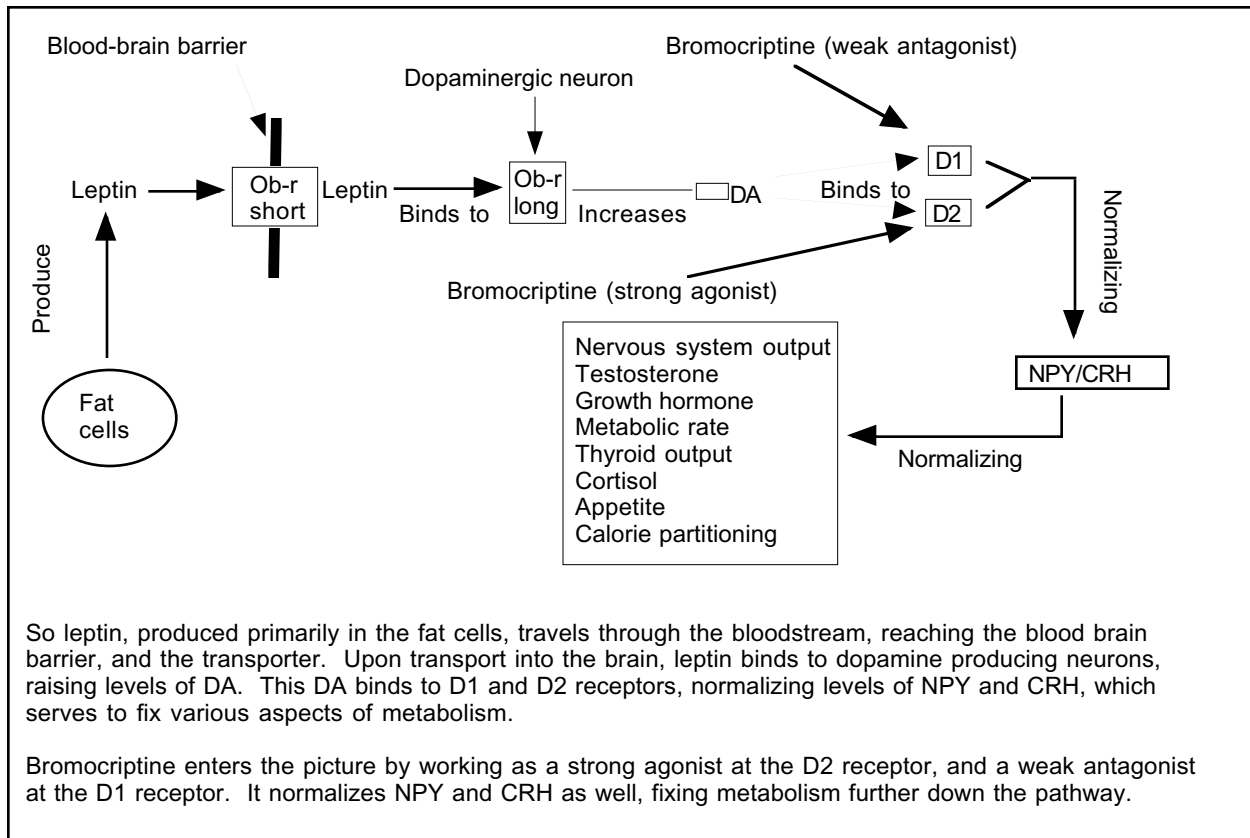
That s the punch line: DA is the link between leptin and metabolism via NPY/CRH. Bromocriptine mimics DA in the brain, making the brain think that all systems are normal even if they're not.

Related to this, I want to mention fat cell apoptosis (death) again. It turns out that injecting leptin into the brains of mice can cause fat cell apoptosis to occur (59). And a recent abstract shows that bromocriptine administration has the same effect (60), once again suggesting that both leptin and bromocriptine are working through the same basic mechanisms. That mechanism is DA. This is all summed up in graphic on page 68.

So normally leptin would bind to the brain, increasing DA levels. That DA would activate D1 and D2 receptors, normalizing levels of NPY and CRH, which would lead to increased metabolic rate, fat burning, testosterone, and thyroid, and decreased cortisol and appetite. When leptin drops, DA levels drop, NPY and CRH go up, and that signals the adaptations to dieting: decreased metabolic rate, crashing hormones, increased hunger, etc, etc.

Since bromocriptine can bind to the D2 receptor, it partially mimics the effects of leptin, correcting NPY and CRH and normalizing metabolism. That's the punch line, bromocriptine allows us to 'trick' the brain into thinking all systems are normal while avoiding the issues of low leptin or leptin resistance.

Figure 1: Proposed Model of Bromocriptine Action



Tying it all together

So that's the proposed model. The next question is whether or not it can adequately explain all the research on animals and humans I've presented to this point. We looked at normal animals (mice, pigs, rats), the OB mouse, post-menopausal women, obese diabetic and non-diabetic men and women. Can the model explain them all?

The OB mouse is easy so we'll start there. Lacking leptin completely, there is no signal being sent to the brain. We'd expect DA levels to be very low (since DA is involved in a lot of other behavioral characteristics, this may explain why the OB mouse tends to sit around a lot). Bromocriptine appears to 'take over' the effects of leptin in the brain, and reset metabolism to normal. While an extreme example, the OB mouse approximates what's going on in very lean humans, who may have levels of leptin so low as to be nearly zero.

Post menopausal women are a bit harder to fit into the model. However, recent research suggests that estrogen deficiency (in rats at least) may cause leptin resistance (61). I already mentioned that aging is associated with leptin resistance, which may be a bigger part of the problem (25,26). In either case, the brain receives less of a signal from leptin. Bromocriptine corrects things (causing major fat loss) by normalizing the signals that leptin should be sending.

Both obese diabetic and non-diabetic humans are easy too. Like the DIO rat (the rat fattened up on a poor diet and no exercise), obese humans (and obesity and diabetes go hand in hand) become leptin resistant with time. This means a lesser leptin signal to the brain, causing characteristic changes in neurochemistry that causes negative things to happen. Bromocriptine tricks the brain and corrects metabolism by mimicking the leptin signal that is not being sent.

I mentioned that injection of leptin into either the brain or bloodstream of certain strains of mice also causes fat cell apoptosis. So does bromocriptine administration. The same improvements in blood glucose, insulin, cholesterol, triglyceride, etc. levels also occur in mice injected with leptin, mimicking the effects seen with bromocriptine in both humans and animals.

So the answer is yes, the model holds for all of the data presented so far. In all cases, leptin and bromocriptine have identical effects, suggesting that they work through the same signaling mechanism, which appears to be DA levels in the brain. Considering the direct link between leptin and DA levels in the brain, the model makes sense.

Summary

Although leptin is still the key regulator in 'telling' the brain what's going on, there are other neurochemicals that leptin ultimately works through. Although there are many already discovered and many more to be found, neuropeptide Y and corticotropin-releasing hormone (NPY and CRH) appear to be two of the main ones. In the various models used, from OB mice to humans, NPY and CRH show characteristic changes in response to such things as dieting and starvation, causing the body to adapt in all the (negative) ways we've talked about. Changes in NPY and CRH affect metabolic rate, hormonal levels, appetite, fat burning, and calorie partitioning. Normalizing levels of those neurochemicals normalizes the rest of the

metabolic picture.

It turns out that NPY and CRH are controlled a little further upstream by levels of brain dopamine (DA). That is, normally leptin would bind to specific neurons, raising brain DA, which would then control NPY and CRH levels. As leptin drops (dieting, OB mouse) or when leptin resistance develops (obese humans, DIO rat), there is less DA produced. This makes the brain 'think' it's starving and NPY and CRH change, affecting everything else downstream negatively. Bromocriptine, by activating the DA receptors directly, can 'trick' the brain into thinking it's not starving, so that the normal metabolic adaptations don't occur. And, finally, that's how bromocriptine works.

Chapter 7: Using bromocriptine, part 1

After all of the previous chapters, you may be a little let down with the actual practical information I'm going to give you regarding bromocriptine, as there's really not too much to it. In this chapter, I want to get down to brass tacks about bromocriptine. I'm going to discuss the practical issues of the different forms of bromocriptine, how to use it, what to expect, and a few other topics.

Had I been a lot lazier, I could have made this one chapter the entirety of the booklet and left it at that. It would have been a whopping 5 pages long. Instead, I wanted to give you the underlying physiology and mechanism. There are two reasons. The first, the one I'm supposed to tell you, is that I wanted to make sure you had all the information necessary to make your own choice about using the drug. The second, and arguably more honest reason, was to justify the cost of the booklet.

To keep the chapter length manageable, I'm going to discuss the side-effects and risk profile of bromocriptine separately in the Chapter 8. I suggest strongly that you read it prior to taking any action. I'll discuss how specific populations might consider using bromocriptine in Chapter 10.

How it's found

Bromocriptine is an extremely common drug, and relatively easy to find. Considering that it's been around for nearly 30 years, and is so readily available, I'd be stunned if there were black market or fakes floating around. Bromocriptine goes by a few other names that you may come across (and of course, there will be country-specific names). Bromocriptine mesylate is the common name and Ergoset (tm) is one of the major brand name versions.

In addition to Ergoset (tm) and Parlodel, bromocriptine is found under a number of brand names including Bromergan, Deprolac, Lactisimine, Parilac, Pravidel, Proctinal, Suplac, and Volbro. Parlodel seems to be the most commonly available brand name and is manufactured by Novartis. Bromocriptine comes in both 2.5 and 5 mg strengths, in either tablets or capsules.

As mentioned in previous chapters, the maximum dose used in human studies

for fat loss or diabetes treatment is 4.8 mg per day (much higher doses are used for other purposes). Of course, this was in leptin resistant (i.e. obese) individuals; it seems possible that lower doses might be effective in others. In that research, there was actually a small percentage of 'fast responders' who got an effect out of lower doses (2.4 mg/day). However, nearly 100% of subjects got an effect out of the full 4.8 mg/day.

This suggests that 5 mg/day is going to be the most appropriate dose for the purposes described in this booklet, mainly to ensure that an actual effect is occurring. That is, while a lower dose (i.e. 2.5 mg/day) may be effective in some people, without blood work (in this case, measuring changes in prolactin), there is no guarantee that the lower dose will be effective. Five mg/day should more or less ensure that some effect is being generated at the DA receptor.

Ordering from overseas pharmacies (easily found on the web), 120X2.5 mg tablets of bromocriptine can be purchased for \$65.00. So a 2.5 mg/day dose would run about 50 cents per day. Five mg would run a dollar per day, less than many supplements and drugs. I would expect bromocriptine to be readily available in Mexican pharmacies, but you'll have to find those yourself.

I should mention that bromocriptine comes in two different forms from Novartis: Parlodel and Parlodel SRO. The SRO form is simply a slow releasing form of bromocriptine, so that single oral doses can be used. Of course there are no studies comparing the two for the uses described in this booklet. For hyperprolactinemia, studies comparing a single oral dose of the SRO form (5 mg/day) to the regular form dosed 2.5 mg twice per day show no major difference in effect (61a, 61b).

However, hyperprolactinemia is characterized by pathologically elevated prolactin levels throughout the day, which is far different than the prolactin profile of otherwise healthy (or even obese/diabetic) individuals. Meaning that it is more important to block prolactin release throughout the day in hyperprolactinemic individuals. This is also a concern for both Parkinson's and Acromegaly patients who need to maintain high, stable DA levels throughout the day.

As I've discussed, this really isn't relevant to the uses described in this booklet. In obese/diabetic individuals, it only appears important to stimulate the DA receptors during the day, as there is sufficient DA stimulation later in the day already. In all of the human studies described, a single morning dose of 2.5-5 mg/day generated all of the beneficial effects that we are interested in. Even in the diabetic studies, where a

faster acting form of bromocriptine, called Ergoset (tm) was used, single morning dosing generated all of the beneficial effects.

Finally, as you'll see in the Appendix, there is no physiological reason to believe that multiple daily dosing (i.e. 2.5 mg at morning and at night) will have any additional benefit for the purposes described in this booklet. Overall this tells me that the choice of form (Parlodel vs. Parlodel SRO vs. Ergoset) should be irrelevant for the purposes described in this book. As long as a sufficient dose (5 mg/day in most people, 2.5 mg/day in a few quick/hyper-responders) is taken in the morning, the beneficial effects should occur.

What to expect: benefits

Make no mistake, bromocriptine is not an instant gratification drug and you should not expect any differently. Bluntly put: bromocriptine is not a magic bullet diet drug. So don't think that taking it is going to be even closely akin to something like clenbuterol or even low dose testosterone, both of which can cause impressive changes in body recomposition fairly quickly even if diet and training aren't modified. The only possible exception is in post-menopausal women (or various animal models) where a single bromocriptine dose each day seems to cause significant fat loss without anything else being done.

As with most drugs, bromocriptine should be looked upon as a support to your training and nutrition needs, not a replacement or substitute. Bromocriptine should improve both the ratio of fat:muscle loss while dieting, as well as preventing the other diet breaker adaptations that tend to occur, such as hunger, metabolic slowdown and all of the rest.

Based on the mechanism of action, I expect that lean individuals using bromocriptine will be able to diet without the major negative effects occurring: metabolic slowdown, muscle loss, hormones crashing, etc. For a contest bodybuilder or lean athlete, bromocriptine should be a nice gray-market way to keep the system humming along while dieting or trying to stay lean.

On that note, bromocriptine is not a scheduled drug (unlike anabolic steroids) nor does it appear on the list of banned substances by the International Olympic Committee, which is generally used by most sporting organizations as the gold

Committee, which is generally used by most sporting organizations as the gold standard for doping. I don't expect that bromocriptine, or other DA agonists, would be tested for but folks involved in competitive sports should make sure and check the specifics of their organizations before using it or any other drug.

I also expect that bromocriptine will allow athletes who are not genetically lean (i.e. most of us) to stay lean while making gains in strength and size. Normally, whenever a natural athlete wants to gain muscle or strength, some fat gain has to be accepted. This is a consequence of the system being so screwed up by low leptin levels. By 'tricking' the brain into thinking that the system is normal, I expect otherwise natural athletes to be able to stay lean and make better gains overall.

I should mention again that bromocriptine appears to have significant benefits for Type II diabetics, or individuals suffering from insulin resistance, by fixing some of the central defects that appear to be part of the problem. Even in the absence of weight/fat loss, bromocriptine at low doses corrects many of these problems, making it potentially extremely beneficial for this group. In fact, the company Ergo Science (<http://www.ergo.com>) petitioned the FDA to allow bromocriptine, under the trade name of Ergoset (tm), to be marketed for this purpose. Although they were turned down (I'll discuss the FDA ruling in the appendix), bromocriptine or other DA agonists represent a potentially novel way of dealing with the increasing problems of Type II diabetes/insulin resistance. As I mentioned a chapter or two ago, as research pinpoints defects in DA levels of DA receptor function as being involved in obesity, you can expect newer DA agonists to be made available for weight loss.

Another potential use/effect of bromocriptine is for bodybuilders coming off of a steroid cycle. One of the most commonly known effects of steroid (and other drug) usage is dysfunction of the Hypothalamic-Pituitary-Adrenal axis (HPA) and the Hypothalamic-Pituitary-Gonadal axis (HPG, called the Hypothalamic-Pituitary-Testicular axis or HPTA in men). Following a cycle, testosterone production is typically reduced, due to a decrease in both leutinizing hormone (LH) and follicle stimulating hormone (FSH). There are also increases in catabolic hormones such as cortisol. Both tend to cause muscle loss and fat regain after the cycle, which is the exact opposite of what bodybuilders want.

As you might guess, elevated prolactin levels can also occur post-cycle which causes more problems such as impaired immune function. Research has also shown that hyperprolactinemia is associated with severe hormonal dysfunction

especially in the HPG/HTP axis and can cause infertility under extreme situations (62,63). While the effects appear most pronounced in women, it wouldn't be surprising if this problem occurred in men as well.

Since brain DA appears to set the normal 'tone' of both the HPA and HPG axis in addition to controlling normal prolactin release, a DA agonist such as bromocriptine should help to normalize the system after a cycle. Using bromocriptine during or near the end of a steroid cycle, most likely in conjunction with other drugs such as Clomid (which kickstarts gonadal testosterone production) and others, should help steroid users to get the system up and running again.

Tying all of this together, you may be wondering exactly what you're supposed to 'feel' while using bromocriptine. Frankly, with the exception of a few minor side-effects, the results will be subtle and fairly subjective. Mainly, because of its effects, I'd expect that problems with hunger and general food cravings should be better controlled while dieting.

If you were measuring morning body temperature (which is a rough measure of metabolic rate), I'd expect it to be maintained far better while dieting with bromocriptine versus without. On top of keeping the fat burning pathways from downregulating, this should allow not only a greater ratio of fat:lean loss, but also an absolute greater amount of fat loss per week to be maintained. Normally, as diets progress, not only is more muscle lost, but the total rate of fat loss per week decreases as caloric requirements go down. By fixing the central defect involved in both systems, bromocriptine should prevent this from occurring, at least to some degree. Maintenance of muscle mass and strength (which are indirect measures of overall body chemistry) should also be improved.

If an athlete wanted to go to the trouble of blood work, the expectation would be that the normal hormone crash (thyroid, testosterone, growth hormone, IGF-1) would be at least partially prevented, even if it's not completely eliminated. Since I doubt that most will go to that kind of trouble or expense, you'll just have to use fat loss and muscle mass maintenance as your guide.

I'd also expect bromocriptine to help with some of the mental problems that occur with dieting such as lethargy, depression and poor mental functioning. Most likely those effects are at least partly related to changes in brain neurotransmitters, as the body tries to get you to sit around more and burn fewer calories. Dopamine (DA) is heavily involved in many other aspects of behavior and brain function and dropping

DA is probably at least partially related to the problems seen. By maintaining a stimulus to the DA receptors, some of these problems should be avoided.

Finally, and somewhat more trivially (or not), bromocriptine may help avoid some of the more negative sexual side-effects associated with severe dieting. A common complaint among both male and female dieters is a total loss of libido, as well as an inability (in men) to do anything even if they want to (I'm talking about impotence, boys and girls). Much of this is hormonal, as changes in testosterone and estrogen affect sexual functioning, but brain DA is also having an effect. Low leptin levels tend to inhibit reproduction (don't want to get pregnant when you're starving) so it's not surprising that overall sexual desire goes down as well.

How to use it

Considering the complexity of the system I described in the past chapters, you're probably thinking that bromocriptine has to be used in some complex stacking or timing pattern. Sadly, no and it's actually pretty simple. As mentioned above, the maximum dose in the human studies to date is 4.8 mg/day and I mentioned that a small percentage of people respond to lower doses. I would be surprised if anybody needed more than 5 milligrams per day. Considering the increasing risk and degree of side-effects with increasing doses (see Chapter 8), I certainly don't think going above 5 mg is a very good idea.

And just because you're a huge athlete or bodybuilder, don't think you need to use more. Your brain is about the same size as everyone else's (insert obligatory joke about athletes and brain size here), even if your body is much larger. Since bromocriptine is working at the brain, you don't need more of it just because you're big.

One important note: bromocriptine is best taken in the morning even if the common recommendations are to take it in the evening. The reason is that normal dopaminergic tone (a techie way of saying dopamine levels) goes through fairly characteristic cycles throughout the day, typically reaching a high in the evening and a low in the morning. Since the side-effects of bromocriptine are related to DA receptor activation, taking bromocriptine when DA is already high tends to make the side-effects worse (on top of being fairly ineffective at increasing the signal being sent to

the brain). Taking bromocriptine in the morning, to coincide with the normal low in DA levels not only minimizes side-effects but provides DA receptor activation when it is needed most.

In addition to the physiological rationale behind morning dosing, I want to mention that, in the human studies which reported positive metabolic results, the bromocriptine was always given in the morning. Side-effects were minimal and transient and results were positive. In the absence of data to the contrary, it seems best to emulate what has been shown to work.

Summary

Bromocriptine is a fairly readily available drug which is reasonably inexpensive. The generic name is bromocriptine mesylate which can be found under a couple of different trade names including Ergoset (tm) and Parlodel. Novartis is the primary manufacturer and costs from overseas pharmacies (which you'll have to find yourself) run about 50 cents per 2.5 mg tablet or capsule. At a daily dose between 2.5 and 5 mg/day, this puts the cost of bromocriptine at 50 cents to a dollar per day.

While bromocriptine isn't an instant gratification type of drug, its biological effects should make it a good adjunct to proper training and diet. If your goal is fat loss, bromocriptine at 2.5-5 mg/day should keep your diet working more effectively and longer, even if it doesn't increase weekly fat loss per se. While 2.5 mg is effective in some people, 5 mg appears to be effective in nearly 100% of individuals and may be a better dose for most individuals. Otherwise 'natural' bodybuilders could use bromocriptine as a gray-market drug to improve overall results, by keeping the system running normally while staying leaner throughout the year.

In addition to both lean and obese dieters and natural athletes, bromocriptine represents an entirely novel approach to treating Type II diabetes/insulin resistance, as it corrects the central (brain) defect causing both problems. Even outside of generating weight/fat loss, Type II diabetics should see improved health indices (decreased fasting blood glucose and insulin, glycosylated hemoglobin, etc) from low-dose bromocriptine.

Most of the effects you can expect to perceive from bromocriptine are somewhat subjective, making it a little difficult to judge what is going on. On top of the side-

subjective, making it a little difficult to judge what's going on. On top of the side-effects (see next chapter), decreases in feelings of hunger, lethargy and depression during dieting would be expected. If you're in the habit of monitoring body temperature, as a rough measure of metabolic rate, I'd expect it to be better maintained overall during dieting. Because of this, in addition to keeping fat burning pathways moving, I'd also expect weekly fat loss to stay at a reasonable level, along with a better ratio of fat:muscle loss.

More detailed blood work, such as measurement of thyroid, testosterone, LH, FSH or others would be a high-tech (and higher-cost) method of keeping track of the system. Keeping track of changes in body composition (weight, fat and muscle) would give you an indirect measure of the same thing. Finally, bromocriptine would be expected to help maintain libido in the face of dieting.

Chapter 8: Side-effects and risks of bromocriptine

Before describing more specific guidelines on how to use bromocriptine for various purposes, I want to take a moment and discuss the side-effects and potential risks of bromocriptine. I want to emphasize how important it is for everyone to read this chapter closely before proceeding.

Drugs and side-effects: general comments

All drugs have side-effects which range from mild to wild. Even aspirin, possibly the most commonly used drug in the world, can cause problems if it is used incorrectly (64). At high doses, stomach ulcers and unstopped bleeding are both risks and deaths due to aspirin abuse have been documented.

Drugs with more profound effects on human physiology can have side-effects that are greater or worse, depending on any number of factors. The point being that no drug you can name, from aspirin to caffeine to clenbuterol to bromocriptine, is 100% safe. There are always risks and the best you can do is determine if the benefits outweigh the potential risks in deciding whether or not to use it.

Some of this is simply a risk inherent to any drug that affects normal human physiology. Stuff that happens in the body generally happens for a reason and mucking about with 'normal' physiology can cause unforeseen problems ranging from minor to deadly. You'll see a really good example of this below when I discuss what happened when bromocriptine was used to stop lactation in young women.

Another part of the problem, mind you, is that most drugs are being used on individuals whose health is not the greatest to begin with. For example, obesity is associated with high blood pressure, and drugs which have further effects on blood pressure (as most diet drugs, which are stimulants, do) can and frequently do cause problems.

More relevant to bromocriptine, diabetes is already associated with a variety of maladies including heart and vascular disease. So it's no real surprise when the occasional problem crops up in this group when they are given a new drug. That doesn't mean that those side-effects can be expected to occur in all or even many

doesn't mean that those side-effects can be expected to occur in all or even many users, or extrapolated to otherwise healthy individuals (such as athletes or bodybuilders). I'll come back to this.

A related, and equally important point that I also want to emphasize has to do with dosing. An old medical homily is that "The dose makes the poison" and this couldn't be any more true when it comes to drugs (or just about anything else for that matter). The dose of a compound (along with other factors such as pre-existing problems and other interactions) has to be taken into account when you consider the overall safety profile. A drug that is exceptionally safe at low doses by itself may become extremely dangerous at high doses by itself, or at low doses combined with other drugs (or other lifestyle factors). I'll address specific cases and examples of this as we go. I urge readers to especially make note of the case-study I describe at the end of this chapter: a sterling example of how an otherwise safe drug can become dangerous when used under the wrong set of circumstances.

In this chapter, I want to discuss the potential side-effects and risks of bromocriptine in some detail. In doing so, I'll be pulling data and information from several sources, which I want to describe up front. Some of it comes straight out of peer-reviewed literature, mainly the data on bromocriptine's use for fat loss or the treatment of diabetes. Since that represents a rather small amount of data overall (5 total studies), I'll also be pulling data from two other primary sources.

The first is a rather standard drug database, available free on the web, called RxList (65). It presents standard data on drug pharmacokinetics, indications, side-effects, etc. I highly recommend that readers use this resource to read up on bromocriptine (or any other drug) prior to use.

The second resource is the transcript of the FDA application proceedings for the use of bromocriptine to treat Type II diabetes (66). Although this doesn't represent a peer-reviewed resource, it does provide a more full discussion of the possible benefits and side-effects that can occur with bromocriptine use. Although it's long and a bit tedious (and their transcription was crappy), I highly recommend that readers check out the information prior to using bromocriptine for any purpose. It's also written in a fairly non-scientific way and should be understandable even if you lack a formal scientific background.

Where the data comes from: overview

Compared to most drugs in existence, because of its age, bromocriptine has a truly absurd amount of research behind it. Since its introduction in the mid-70's, roughly 2400 scientific papers (in adult humans) have appeared on Medline regarding bromocriptine. This represents an enormous number of subjects. There's no real way to tell how many bromocriptine doses have been used over the nearly 30 years of its use but it's likely in the millions.

Over that 30 years, bromocriptine has been used to treat three primary conditions, which I mentioned a chapter or two ago. The largest group, and the group that uses doses the closest to what's being described in this booklet are individuals with hyperprolactinemia. Typically, doses of 2.5-7.5 mg/day (with a range of 2.5-15 mg/day) are used in this group (67). This is the group that I'll pull the majority of safety and risk data from.

A second, and smaller group, and one which uses much larger doses and has its own severe set of problems are Parkinson's patients. These folks use up to 40 mg/day of bromocriptine in conjunction with multiple other drugs. A third, and even smaller group are folks suffering from acromegaly, who may use doses of 100 mg/day or higher. Due to the massive doses used, and the pre-existing pathologies that are already present, I don't consider them representative of the doses described in this booklet. I'll only make brief mention of them.

The final group, and the one that we are most interested in, but which has the least amount of data, are obese diabetic or non-diabetic men and women, in whom bromocriptine has been studied for potential fat loss and anti-diabetic effects. This data spans multiple studies and over 1000 subjects given bromocriptine (compared to 400 given the placebo) so keep that in mind when I talk about the absolute number of major events. I also want to mention that many of these diabetic subjects were also on other diabetic drugs at the same time. Whenever more than one drug is being used, especially in a group with pre-existing health problems, the potential for a negative interaction also increases so remember that as I discuss some of the negative occurrences.

Minor side-effects from bromocriptine

Minor side-effects from bromocriptine

Like most drugs, bromocriptine can cause a number of minor side-effects which I'll discuss in this section. In folks treated for hyperprolactinemia, the minor side-effects are (in decreasing order of frequency) nausea, headache, dizziness, fatigue, lightheadedness, vomiting, abdominal cramps, nasal congestion, constipation, diarrhea, and drowsiness. The statistics on each side-effect, in terms of how frequently they occur (in terms of percentage of subjects), can be found by checking RxList (68).

I want to mention that all of these effects are related directly to DA receptor activation, that is the drug's main mode, and our desired mode, of action. As mentioned last chapter, this is why taking bromocriptine (or any DA agonist) at night tends to cause more and more severe side-effects: DA is generally higher in the evenings, so further activation of the DA receptor with bromocriptine tends to increase the number and severity of side-effects (without really increasing the benefits of the drug).

Taking bromocriptine in the morning, when DA is low minimizes the side-effects because you don't over-activate the DA receptor. That's on top of maximizing the beneficial effects since these are also generated by activating the DA receptor when DA is low.

In any event, with bromocriptine use, one or more of these minor side-effects are typically seen in a majority (70%) of users. Typically, only 5% of the total users examined have to discontinue use entirely. Frequently, lowering the dose for a few days allows even those individuals to continue use (68). I should mention that, for whatever reasons, women seem to be slightly more prone to side-effects than men (66, pg. 108). Do note that these minor side-effects also tend to go away rapidly, usually after the first few days/doses of the drug.

Although extremely rare, I should mention that a few cases of cerebrospinal fluid rhinorrhea (a discharge of cerebrospinal fluid from the nose) have been reported in patients receiving bromocriptine for treatment of large prolactinomas (prolactin-producing tumors). It should be pretty clear that this side-effect is of no relevance to folks lacking such tumors.

Overall, considering its length of use, bromocriptine is still considered the primary treatment option for hyperprolactinemia and has a long history of established

safety and use (69). In both Parkinson's and acromegaly patients, the side-effects tend to be greater, because of the larger doses used, so I'll discuss them in the next section.

The final group of interest are obese diabetic and non-diabetic individuals who have been studied for fat loss and improvements in Type II diabetic complications. In those studies, the commonly reported side-effects were the same as what was seen in individuals treated for hyperprolactinemia (66, pg. 106). An additional side-effect, most likely due to the changes in insulin sensitivity and glucose uptake was hypoglycemia (low blood sugar), ranging from mild to major. To quote the researchers, from the FDA docket:

"The most serious reported hypoglycemia, which is not a serious adverse event but classified on the mild, moderate, severe type classification of an adverse event, was treated with a piece of candy and resolved." (66, pg. 109)

That's right, the most severe hypoglycemic reaction was dealt with with a piece of candy. Pretty deadly stuff, this bromocriptine. And even then, the incidence of hypoglycemia wasn't significantly different in the bromocriptine group versus the placebo group (66, pg. 108), being that a hallmark of diabetes of poor blood glucose control.

On a more serious note, I want to mention this potential side-effect due to the popularity of low-carbohydrate diets, which tend to lower blood glucose slightly as well. If you're using a low-carb diet or are involved in heavy exercise (which tends to improve insulin sensitivity and lower blood glucose concentrations) you need to be aware of the possibility of a hypoglycemic reaction if you choose to use bromocriptine. Crashing blood glucose can cause dizziness, nausea and sweats at the least, and unconsciousness or coma in extreme circumstances. Raising total daily carbohydrate intake may be necessary if you choose to use bromocriptine, so be aware of it.

A drop in blood pressure (hypotension) is another commonly reported side-effect, one that can actually be beneficial in some situations. Although typically small (~ 5 mm Hg), this change can be significant for some individuals. In fact, in one of the studies of obese individuals, the drop in blood pressure was actually beneficial as many of the obese individuals were able to discontinue their blood pressure

medications (35).

For folks with normally low blood pressure, the drop can cause transient fatigue and lightheadedness (love that head rush). Again, this is something to be aware of, especially if you're dieting or on low-carbohydrates, both of which tend to lower blood pressure as well.

Major side-effects from bromocriptine

In addition to the minor side-effects discussed above, there are a few potential, but rare, major side-effects that I want to discuss for completeness. These include a handful of deaths. I want to make it clear that in, most of these cases, the major side-effect was as much a consequence of something else (i.e. pre-existing pathology or disease) as of the drug itself. I'll discuss each case individually.

On that note, I should mention that the occasional death due to abuse is common for just about any drug you can name so bromocriptine is no different in this regard. Even aspirin, one of the more innocuous drugs, has caused a number of deaths, usually when it was used incorrectly or at abuse level doses. Even at therapeutic doses (1000 mg/day) aspirin can cause severe problems such as stomach ulcers and runaway bleeding (64).

So the occasional major side-effect or death is nothing new when it comes to drugs; they all cause the occasional unexpected problem to crop up under the right combination of circumstances. The real question is whether the drug itself is increasing the risk of problems to such a degree as to make its use overly dangerous.

Although I said that I don't consider it a very relevant population, I want to mention that high doses of bromocriptine, as seen in Parkinson's and acromegaly treatment (doses of 40-100 mg/day are used) can cause hallucinations and severe dizziness (68). Since bromocriptine is an ergot derivative (like LSD), this is no huge surprise. Other, more severe side-effects are also seen in these populations (68). Considering the preexisting health problems, as well as the massive doses being used (approximately 15 to 25 times the doses described in this booklet), I also consider them irrelevant to what's being discussed in this booklet.

To get it out of the way I want to mention a situation where bromocriptine use in

To get it out of the way I want to mention a situation where bromocriptine use in a specific population may have contributed to a number of deaths. At one point bromocriptine was used to stop normal milk production (by shutting down prolactin production) in young lactating women, and the drug may have contributed to the 19 deaths due to heart attack, stroke, or seizures (66, pg 137). In the same population (young women given bromocriptine to suppress lactation), various cardiovascular events have also occurred.

Considering the rather massive hormonal changes which occur during pregnancy and lactation, giving a drug to women that alters or stops those changes is sort of silly in the first place. Giving postpartum women a drug to shut down normal physiology (lactation) is going looking for an accident. Even then, it was never shown conclusively that the drug itself was the cause of the death; Sandoz (which was producing the drug at the time) pulled the drug voluntarily from the market in 1994 just to be safe (66, pg 137).

In one of the bromocriptine diabetic studies, there were also two subjects (again, out of 1000 total subjects) who showed evidence of impaired liver function (66, pg 110-111). Note that Type II diabetes is associated with liver problems (called a fatty liver, due to the overaccumulation of triglyceride in the liver) in the first place and the first of these subjects was, in fact, diagnosed with a fatty liver. The cause of the second subject's problems were never determined but they were taken off the drug immediately and liver function returned to normal within 4 weeks, indicating that any problems were reversible (66, pg. 111).

The final, and perhaps most sobering major risk factor also occurred in the diabetic studies: myocardial infarction ("MI", aka a heart attack) (66, pg. 112). Over the span of the three studies (and over 1000 subjects, recall) looking at bromocriptine use in diabetics, there were a total of 12 myocardial infarctions compared to 2 or 3 in the placebo group (do make note that even the placebo group had problems). First and foremost, you have to realize that coronary artery disease (the root cause of heart attacks) is the leading cause of death in diabetic patients in the first place; so heart attacks in this population are to be expected, drugs or not.

The bigger question, and one examined in detail in the FDA docket is whether or not the bromocriptine increased the risk of MI in otherwise at-risk individuals. To examine this issue, the researchers at Ergo Science did a detailed statistical analysis (described fully in the FDA proceedings) and concluded that the bromocriptine did

NOT increase the risk of MI, even in diabetics with pre-existing cardiac conditions. That is, there was no greater incidence of MI than you d expect in a diabetic population in the first place and the MIs were a consequence of the diabetes, not the drug. In this regard, the researchers state:

"So since the observed MI rates were comparable or lower than the reference population of type 2 diabetes and similar to placebo in all clinical studies, I concluded that there was no evidence to support a causal association between Ergocet™ and an increased risk above the endemic rate in patients with diabetes for cardiovascular adverse events." (66, pg. 119)

Additionally, in looking at all of the cases of MI, the researchers state:

"And when we looked through the individual case histories it's really pretty clear that this is what you would expect in a group of patients with diabetes. Many of them had extensive coronary disease, previous bioplast graft surgery, or when they had their infarc they went to angiography and then had extensive disease and underwent PTCA." (66, pg. 120)

Which, roughly translated into English, means that the few MIs which did occur in the diabetics given bromocriptine were not a surprise considering the population. The bromocriptine group showed either the same or a slightly lower incidence of MI than you'd expect to see in diabetics in the first place. Conclusion: the bromocriptine itself did not contribute, there were severe preexisting health problems which contributed to the overall risk.

Related to this, we might consider that in Parkinson s and acromegalic patients, who are given much higher doses of bromocriptine, there has been no report of increased MI risk. It seems difficult to conceive of a situation where 5 mg/day of bromocriptine would increase the risk of a MI while 40-100 mg/day would not. Simply put, few drugs become safer at higher doses. Considering the known risk of an MI in a diabetic population, the logical conclusion is that the disease, and not the bromocriptine was the cause of the MIs in these studies.

A few comments in summary

Following up on the side-effects and safety data above, I want to refer to two reviews of safety data on bromocriptine. As I mentioned early in this book, bromocriptine has been in clinical use for nearly 30 years, having been introduced for hyperprolactinemia in the 70's. In the mid-80's, two reviews were published on the overall safety of bromocriptine over the previous 10 years of use (69,70).

The first review dealt primarily with the use of bromocriptine in females with hyperprolactinemia (69) and concluded that its use was associated with no serious negative effects for either the women being treated or their offspring (noting that bromocriptine was being used to fix fertility problems).

The second, and perhaps more interesting review covered the long-term use of bromocriptine over 1 to 10 years of use (70). It examined the data on 1100 individuals who had been on bromocriptine from 1 to 10 years at doses ranging from 1.25 to 80mg/day. It also looked at data on 700 individuals with Parkinson's disease using doses from 3.75 to 170 mg/day and in 28 patients with other conditions at doses of 2.5 to 20 mg/day. So that's over 1800 people who were on doses of bromocriptine varying from small (1.25 mg) to huge (170 mg) over a span of 1 to 10 years.

The conclusion of this paper pretty much sums it up so I'll quote it in full:

"The side-effects of long-term bromocriptine treatment are virtually no different from those seen during short-term treatment; most of them are relatively benign, and they have been shown in virtually all patients to be reversible. Bromocriptine appears to have no harmful effects on hepatic, renal, hematologic, or cardiac functions. It is considered that a hitherto unknown, severe though rare side-effect of bromocriptine is unlikely to be reported after such long experience." (70, pg. 25)

Simply put, after so many years of research and clinical use, if bromocriptine weren't extremely safe at the low-doses used for hyperprolactinemia (which are similar to the doses described in this booklet for body recomposition or diabetes treatment), we'd know about it by now.

Minimizing side-effects and risk

In practice, avoidance of the minor side-effects is best accomplished by starting with a partial/low dose and increasing every 3-7 days until the full desired dose is reached. In the diabetes studies, starting with that low dose and building up avoided most of the side-effects that typically occur. Proper timing is also a key to minimizing the side-effects. I've mentioned once or twice that bromocriptine should be taken in the morning but want to reiterate it here. Taking bromocriptine at night will tend to maximize the side-effects without really doing anything to improve the benefits.

Additionally, considering the effects of bromocriptine in slightly decreasing blood glucose, taking bromocriptine with meals, preferably with at least a small amount of carbohydrates should help to limit problems. Obviously, dieters who are training intensely (think contest bodybuilders or other athletes) should be even more careful. Overtraining can throw off normal physiology and cause dehydration, fatigue, low blood glucose, etc. when combined with dieting. Adding bromocriptine to the mix could potentially make that worse (see the final section of this chapter for a sterling example of how not to use bromocriptine).

No woman should be dieting while she's pregnant or lactating in the first place, and using a drug like bromocriptine (or most drugs for that matter), with rather profound effects on any number of physiological systems would be extremely silly. That is, unless the drug had been shown to be extremely safe under those conditions. Although bromocriptine was never implicated as the cause of death in lactating women, the potential risk is simply too high for any benefit which might accrue. Put as directly as possible: don't even think about taking bromocriptine if you are or might be pregnant or lactating.

Although the few heart attacks occurring in the diabetes studies were not linked to bromocriptine per se, it should go without saying that anyone with any type of pre-existing disease (diabetes, heart disease, etc.) should be under full medical watch before they take bromocriptine or any other drug. Monitoring health status through regular blood work is the only reliable way to avoid a potential problem and this requires regular visits to a physician. In actuality, all individuals, even those without (or unaware of) a pre-existing problem should also be under a doctor's guidance prior to using bromocriptine or any drug.

Now before anyone gets the wrong idea, the above paragraph could be written

Now before anyone gets the wrong idea, the above paragraph could be written for any drug anybody cares to name. Aspirin, alcohol, ephedrine, caffeine, you name it; there's always a slight risk that something very bad will happen under the right set of circumstances. The question is always whether that risk outweighs or is outweighed by the potential benefits. If the potential benefits greatly outweigh the risks, the drug is probably of use. If the risks greatly outweigh the benefits, it's probably not. If the risk to benefit ratio is close, the choice becomes much harder. Ultimately, that choice should be made by the individual, based on their own study of the information at hand.

In terms of bromocriptine specifically, there appears to be minimal risk and only minor side-effects when it is used properly at low doses. Obviously, those risks and side-effects increase with higher doses and/or when there are pre-existing pathologies present. Whether the benefits (observed or speculated) of bromocriptine outweigh those minor side-effects and slight risks is ultimately up to the decision of the reader.

Finally, I feel compelled to make the following statement specifically in regard to bromocriptine: if for any reason you feel that the side-effects (at any dosage) are more than your body can handle, the drug should be discontinued immediately. Basically, if your body is telling you to stop using the drug, you should probably listen to it.

Once again, this statement could be made for any drug out there: if you are sensitive to the side-effects and they are doing more harm than good, the drug should be stopped. As a random example, as much as I think ephedrine and caffeine are an excellent tool for fat loss during a diet, some people simply can't handle the side-effects, meaning that they should discontinue its use immediately. Bromocriptine (or any other drug) is no different in this regard: if the side-effects are intolerable, the drug should be discontinued.

For reference, bromocriptine reaches peak blood levels ~2-3 hours after ingestion, and has a half-life in the body of approximately 15 hours. The majority of a single oral dose will be eliminated in roughly 30 hours and any side-effects would be expected to disappear at that point as well. So if you feel that bromocriptine is causing more harm than good, you should be back to 'normal' within 30 hours following your last dose.

Drug-drug interactions

Another topic I wanted to discuss briefly is the possibility of interaction between bromocriptine and other drugs. Oddly, despite 30 years of research, there has been scant study of how bromocriptine might interact with other drugs so much of what I'm going to write is sort of speculative, based on what little data is available.

About the only good data on potential drug interactions has to do with alcohol (which can potentiate the side-effects of bromocriptine, and other dopamine agonists). So mixing alcohol and bromocriptine is a no-no. Because of its close structure to ergotamine derived drugs, such as LSD, bromocriptine should not be taken with those types of drugs either either.

Beyond that limited information, there simply isn't much data on potential drug-drug interactions. However, in their research on the compound, the company Ergo Science (which applied to the FDA for a new use patent on bromocriptine, see the appendix for the details) did some metabolic research on the metabolism and handling of bromocriptine in the body.

The first observation they made was that bromocriptine is exceptionally non-liver toxic (recall that the two liver complications reported above were due to pre-existing diabetic pathologies; they were not related to the bromocriptine itself). With *in vitro* work they showed that there is no indication of damage to liver cells at concentrations representing maximum plasma levels of the drug (which someone taking 5 mg/day wouldn't come close to) (66, pg. 186).

The second observation they made was that bromocriptine is handled in the liver, metabolically, exclusively by the class of enzymes called cytochrome P450 oxygenases. Without getting too detailed, the cytochrome P450 system is responsible for degrading many compounds in the liver, although there are other systems present as well (66, pg. 183-187). This means that any potential interaction with other drugs would be for drugs that also are degraded by the same cytochrome P450 system.

This includes a rather broad spectrum of compounds and I highly recommend that anyone who is even remotely considering stacking bromocriptine with another drug check out that drug on Rxlist (65) or another standard drug reference to see if it is metabolized by the same metabolic pathway. If so, the potential for an interaction in terms of liver problems exists.

Additionally, using another drug that activates the Cytochrome P450 system may change how much of the bromocriptine gets into the bloodstream (because less would be degraded in the liver), which would affect dosing. The take-home message is to do your homework anytime you even think about combining different drugs. As a random example, alcohol plus ibuprofen, both of which affect liver metabolism can cause pretty severe problems; you run the same risk with any other drug combination as well.

A note in closing

I have gone out of my way to try and make this booklet as objective and unbiased as possible, by presenting all of the data behind both the risks and potential benefits of bromocriptine. I bring this up because the topic being discussed, a drug for body recomposition (and other) purposes that is not approved for such uses, is always a sketchy one.

Whenever drugs are discussed, especially in the US, especially for weight loss, there tends to be quite a bit of hysteria, over-reaction and downright hypocrisy involved. A recent example involves the FDA's case against the use of ephedrine. A handful of deaths, which were almost exclusively relegated to individuals with preexisting conditions or who abused the compound (or used it with other drugs) have whipped people up into an anti-ephedrine frenzy. This is disingenuous on the part of the FDA as ephedrine has been shown to be safe and effective *when used properly* in dozens of studies over a decade. But scare tactics always seem to work better than objective reporting in these situations.

At the same time, the FDA will frequently give approval to drugs with known risks or side-effects, without making an issue out of them at all. Basically, there is little consistency in the way that drugs are reported on, and individuals can take whatever personal bias or beef they have with a drug (or individual) and mis-represent the data.

The point I'm trying to make is this: you can make a drug appear safer than it really is, or much more dangerous than it really is, with selective data presentation. Taking data out of context, or presenting it partially can really color what conclusion you lead people to. As a specific example, consider the handful of heart attacks that

you lead people to. As a specific example, consider the handful of heart attacks that occurred in the diabetics given bromocriptine. Someone could easily point out that Bromocriptine caused 12 heart attacks and make the drug sound extremely dangerous. It's only knowing the full story, that the heart attacks occurred in diabetics with severe pre-existing heart disease, and that there were a number of heart attacks in the placebo group as well, that the true story emerges.

As much as possible, I've tried to present the data as completely as possible, both in terms of risks and benefits. Even so, that doesn't mean that someone couldn't pull a scare-tactic piece on bromocriptine with selective editing or data presentation. It's fairly easy to do.

Since a detailed discussion of how people can perform this kind of smear campaign is outside of the scope of this book, I'd like to refer readers to an excellent article already available on the web. While it deals primarily with anabolic steroids, the principles and concepts are identical (especially note the comparison between liver problems associated with steroids and Ibuprofen and the difference in public/official opinion about the relative risks of each drug). The article was written by John Williams, JD and can be found at the following link:

<http://www.meso-rx.com/articles/williams/demonization-of-anabolic-steroids-01.htm>

Summary

As with any drug you can name, bromocriptine can cause a number of minor and major side-effects which occur at varying frequencies. Minor side-effects occur in a majority of individuals at low doses and include nausea, headache, dizziness, fatigue, lightheadedness, vomiting, abdominal cramps, nasal congestion, constipation, diarrhea, and drowsiness. Typically these side-effects are minor and transient, going away within a few days of use.

Another reported side-effect is hypoglycemia (lowered blood glucose), most likely caused by the improvement in insulin sensitivity and glucose uptake into cells. The effects are mild but people using low-carbohydrate diets or involved in heavy training should be aware of it. Carbohydrate intake may need to be increased to compensate. Another common side-effect is a slight decrease in blood pressure;

which can actually be beneficial for folks with high blood pressure, but could cause problems for folks with normal or low blood pressure.

At the higher doses (40-100 mg/day) seen in Parkinson's patients and acromegalics, side-effects include dizziness and hallucination but the doses used make these effects irrelevant to the being described in this booklet.

A few other major problems have occurred but they are very rare. In the 80's, bromocriptine was used to inhibit lactation in pregnant women and was associated with a handful of deaths but a direct link between the drug and the deaths was never proven. In addition, in the diabetic studies, there were 2 cases of liver problems out of over 1000 subjects studied. The first was related to the diabetes itself, the second's cause was never determined but the problem went away within 4 weeks of being off the drug.

Finally, and perhaps more importantly, in the diabetic studies, there were approximately a dozen occurrences of myocardial infarction (heart attack). Once again, this represented 12 occurrences out of 1000 subjects studied, noting that heart disease is a common and major complication of diabetes in the first place. There were a handful of heart attacks in the placebo group as well. After detailed statistical analysis, it was determined that this number of heart attacks was no greater than you'd expect in a diabetic population in the first place and analysis of the health-histories showed severe pre-existing heart disease to begin with; the diabetes, not the bromocriptine, was to blame. Considering that heart attack hasn't been observed in Parkinson's or acromegaly patients on much higher doses of bromocriptine, it seems unlikely that the bromocriptine could be to blame. That is, if 40-100 mg/day isn't causing heart attacks to occur, it's difficult to see how 5 mg/day could suddenly become lethal.

Overall, in its nearly 30 years of use, bromocriptine has shown an amazing benefit to risk profile, causing a number of minor, well-tolerated, and transient side-effects along with an even vanishingly smaller number of major side-effects. It is still considered the primary treatment option for hyperprolactinemia and has shown both short- and long-term safety over nearly three decades of use.

A last-minute addition: Bodybuilder screws up

Just as I was completing this booklet, a case study of a bodybuilder who ran into problems while using bromocriptine appeared in the British Journal of Sports Medicine (71). The case study literally reads like a shopping list of how NOT to use bromocriptine.

Over a whopping 2 page case report (which was mainly designed to generate some fear about internet drug sales), researchers describe a bodybuilder in contest training who had two fainting episodes (called "syncope") at home, leading to facial cuts. He had a third episode, lasting a few seconds in the emergency room. After discontinuing the bromocriptine, he had two more short episodes of syncope within the next 24 hours, also while in the emergency room.

While he was in atrial fibrillation (an abnormal heart rhythm) during this time, all other measurements, including heart rate and blood pressure were normal and he showed no signs of heart dysfunction or any abnormal neurological signs. A followup stress test (Bruce protocol) showed no problems.

Upon examination, he reported taking low dose bromocriptine (2.5 mg/day) along with anabolic steroids (Dianabol, 5 mg four times per day) and was on a "strict diet". No other drug use was indicated although it's common knowledge that contest bodybuilders take far more than what was reported in this paper. Before we draw any conclusions about the risks of bromocriptine from this single report in a single individual, let's look at the entire story.

He was described as having no pre-existing health problems beyond a family history of ischemic heart disease (meaning blockage of the coronary arteries), reported having worked unusually long hours, took the bromocriptine at night (10 pm) after skipping his normal evening meal, and had skipped breakfast the morning after taking the drug (but took his normal anabolic steroid dose that morning).

This was on top of being in the middle of contest training, which is as intensive as it gets. It's not uncommon for bodybuilders to faint during contest dieting while taking no drugs; it happens when you push the body too far, sometimes. No details of his training were given but you can usually assume near daily weight training and cardio done once or more times per day for contest bodybuilders.

Ok, without even saying anything else, it's pretty obvious that this guy fucked it up pretty badly. First, he took the bromocriptine at night, which I have stated multiple

times will make potential side-effects much worse. Dizziness and lightheadedness could turn into fainting if pushed to the extreme and that's likely what happened. Second, he skipped multiple meals (dinner and breakfast) while working long hours and involved in contest preparation (which is extremely strenuous as it is). Skipping meals in the middle of a contest diet is a great way to put yourself down in the first place, because blood glucose crashes. Considering the potential hypoglycemic effects of bromocriptine, skipping meals while taking it is a huge mistake.

The authors concluded (71, pg. 67) that "[a]lthough the dose taken by the patient was relatively low, the side-effects were probably potentiated by a combination of a very strict diet, taking bromocriptine (from a dubious source) in a fasting state, working excessively hard (with increased vagal tone associated with his bodybuilding activity), and taking high doses of anabolic steroids." Lemme explain the key parts of this quote.

Increased vagal tone means that the heart is receiving higher than normal signals (via the vagal nerve), and is indicative of the high levels of stress (contest dieting + contest training + long work hours) that this guy was under. Overtraining plus skipping meals plus working long hours is going to screw up normal physiology, because of the stress response that is going to occur.

We might question the use of the phrase 'high doses of anabolic steroids' to refer to 20 mg of dianabol per day by itself, but the rest of it is the key stuff. It was the combination of factors that caused this guy to go down; not the bromocriptine per se.

The 'dubious' source comment on their part has to do with their attempt to rile up some fear about internet drug sellers. There is also the possible inference that the bromocriptine he got was tainted or impure in some fashion.

Basically, as with all of the data I've presented on the safety of bromocriptine already, it was the combination of factors (and several major fuckups on the part of this guy) that caused this problem. Taking bromocriptine at night is looking for problems in the first place; taking it at night and skipping meals, while stacking it with other drugs, while in contest training, while working long hours is really looking for trouble.

As the old saying goes, when you go looking for trouble, eventually you find it. This guy found it.

Chapter 9: Using bromocriptine, part 2

Now that I've given you all of the facts about potential side-effects and risks, I want to discuss some specific groups and how they might best use bromocriptine to meet their goals. In all honesty, most groups would use bromocriptine in basically the same way (in terms of dosing, timing, etc.). The biggest difference would be in the rest of what they were doing, so that's more of what I'm doing to discuss below.

If you're dieting

As I mentioned, with the exception of post-menopausal women, bromocriptine does not appear to generate fat loss unless it's used in conjunction with a below-maintenance calorie diet (or a maintenance calorie diet with exercise). In the studies where calories were kept at maintenance, even though there were health benefits, no fat loss occurred. I said it above, but it bears repeating: bromocriptine is not a magic bullet drug that can replace proper dieting or exercise; it is an adjunct to make the diet and/or exercise program work more effectively in the long-term.

So using bromocriptine for dieting purposes requires that you first set up a good below-maintenance calorie diet. If you're expecting me to now hand you the Magic Bromocriptine Diet Plan (tm), you're mistaken. Outside of making sure that it's below maintenance, has adequate protein, and sufficient dietary fats, I don't think diet composition makes that much of a difference. Not as much difference as I'd like anyhow. The studies used a 30% calorie deficit which I consider a bit excessive except for the obese (>25% bodyfat for men, >30% bodyfat for women).

Leaner individuals would be better served starting with a 10-20% caloric deficit and exercise. In practice, a caloric intake of 10-12 calories per pound of current bodyweight is about right for most people. That along with regular weight training and cardio is about ideal for fat loss without too much muscle loss.

All dieters should set protein at around 1 gram per pound of lean body mass to help limit muscle mass loss. A fat intake of 15-25% of total calories should be considered a bare minimum (for a variety of reasons beyond the scope of this book) and most of those fats should come from healthy sources such as olive oil, flax oil, and fish oils (taken as 6X1 gram capsules per day). The rest of the diet would be

and fish oils (taken as 6X1 gram capsules per day). The rest of the diet would be carbohydrates, preferably from unrefined, high-fiber sources. Other diet interpretations (such as keto or Zone type diets) would probably work just as well. As long as they are below maintenance calorie-wise, have adequate protein and essential fatty acids, I just don't think it matters for most people; pick something you can stick with. If you need more detailed information on how to set up a fat loss diet, see my first book (72) or any number of internet postings on the topic (you can use the same Google search engine mentioned below).

The reason I'm not making a big deal about diet in terms of bromocriptine is that, while you can affect brain chemistry to some degree with diet, it's just not that significant. On any below-maintenance calorie diet, leptin drops, and dopamine (DA) will drop too. Bromocriptine helps to correct the DA drop, to prevent the brain from noticing that it's starving to death and adapting, and that's that.

One consideration regarding a fat loss diet might be the supplement synephrine which, as discussed previously, is an alpha-1 agonist. Use of synephrine should improve leptin transport across the blood brain barrier which may also benefit a diet. Do note that synephrine will also cause vasoconstriction (a decrease in the diameter of blood vessels), and has the potential to raise blood pressure for this reason.

Something else I want to mention here (I'll mention it again next chapter) has to do with one of the more common dieting drugs, the ephedrine/caffeine (EC) stack (the following comments would also include the drug clenbuterol). While EC is an excellent adjunct to a fat loss diet, and has been proven in numerous studies to improve fat loss, ameliorate the drop in metabolic rate during dieting, and help in sparing muscle mass, it can't be used with bromocriptine.

As it turns out, beta-agonists (or sympathomimetics to be more accurate) block the effects of bromocriptine (73, 66 pg. 75-76), so the two can't be combined in a dieting stack. Considering that bromocriptine should prevent the normal drop in metabolic rate, fat burning, etc. that the EC stack was fixing, this shouldn't be a huge issue. With bromocriptine, you no longer need the EC stack anyhow.

About the only other consideration is a strategy I mentioned obliquely in an earlier chapter: high-calorie, high-carb refeeds can bump leptin back up, and we would expect that to bump DA up as well. This seems to help keep the body from adapting as quickly to the diet, keeping all systems running. If nothing else, allowing

a relatively non-diet day helps deal with the psychological aspects of dieting, namely deprivation.

If you're familiar with my various internet writings, you already know about refeeds. If not, the basic gist is simple: every once in a while during your diet break the diet and go nuts with raised calories (10-20% above maintenance calories) and high carbs. On refeed days, you should reduce fat intake to about 15% of your total daily calories and keep protein constant at about 1 gram/pound of lean body mass.

If you're wondering how often to refeed, once per week is about right for most people. If you're very lean you need to do them slightly more often; if you're fatter, a little less. The details are beyond the scope of this book but, if you're on the net, surf over to http://groups.google.com/advanced_group_search and search the newsgroup misc.fitness.weights for posts on leptin or refeeds by either myself or Elzi Volk.

If you're training intensely (and anyone dieting should be exercising in the first place), put the refeed day on one of your weight workout days. If you're not training (shame on you), schedule the high calorie day whenever it fits your social calendar the best.

If you're a diabetic

Although I didn't talk about it in huge detail, bromocriptine appears to correct many of the defects inherent to diabetes, without affecting bodyfat levels. This is a little bit unusual since the interventions that improve diabetic parameters typically go hand in hand with changes in bodyweight. Apparently bromocriptine is an exception to this. For whatever reason, it corrects some of the defects, without generating measurable fat loss.

Another interesting facet of bromocriptine for diabetic complications is that it works centrally, at the brain. Most diabetic drugs act at the pancreas, muscle, or fat cells, to try and fix the myriad problems; bromocriptine fixes the problem at the level of the brain, making it more exciting in a lot of ways. In any event, if you're diabetic (or even severely insulin resistant which is a pre-diabetic state) and only interested in improving your health without worrying too much about fat loss, bromocriptine may help.

Of course, losing weight/fat with a change in diet or exercise should always be part of the overall treatment of insulin resistance/Type II diabetes, but bromocriptine has benefit even without them (noting that the diabetic population is one of the worst when it comes to actually dealing with their disease, preferring to take more drugs rather than change lifestyle habits).

Again, 2.5-5 mg/day, taken in the morning is what's been used in the studies and appears to have the same minor, transient side-effects seen in everyone else. Since most diabetics are (or should be) monitoring their health with regular blood work (glycosylated hemoglobin, fasting blood glucose, etc.), they should be able to judge if the bromocriptine is working or not. Once again, considering the other health problems associated with the disease, all diabetics should be under close physician care. Obviously, the use of bromocriptine for diabetic treatment should be discussed with your diabetic care provider.

If you're a lean athlete who wants to build mass

Another group who should be able to benefit from bromocriptine, at least in theory, are lean athletes or bodybuilders who want to make size or strength gains without putting on too much bodyfat. This effect would occur via the correction of NPY and CRH levels, to affect overall nutrient partitioning, by pushing more calories towards muscle, instead of towards fat cells.

Of course, using bromocriptine would certainly be against the moral stances of anyone who wanted to be completely 'natural', but individuals who wanted a gray-market drug that improved their results without going the route of anabolic steroids or other controlled substances may find bromocriptine to be useful. As mentioned in a previous chapter, bromocriptine isn't scheduled and doesn't appear to be tested for by the major sporting organizations. So a 'natural' athlete could take it without fear of failing a drug test. You can let your own moral stance determine your choice from there.

Under most normal circumstances, whenever you try to gain mass, you must eat a surplus of calories. Because of the dynamics of the body, some portion of those calories will almost always end up as bodyfat. Ratios of muscle to fat gain vary depending on genetics and other factors, but many athletes report a gain of about 1

pound of fat for every one pound of muscle when they are very lean.

This has to do with all of the hormonal dynamics that I bored you with in the first few chapters, along with a few others. This is referred to as calorie partitioning and I already mentioned that correcting the levels of NPY and CRH helps to partition calories away from fat cells. Since regular training (weight training) improves the body's ability to store calories in muscle cells, those calories not going to fat cells should go to muscle cells. Viola, less fat and more muscle gained.

Since the fat has to eventually come off, that makes getting big and lean a process of two steps forward and one step backward. Gain some muscle, gain some fat; lose the fat and try to hold on to the muscle. Over time, this adds up to significant muscle mass gains. It's tedious and less than ideal in the long run; it's simply the best solution to date. I would expect bromocriptine to shift those ratios toward more muscle and less fat gain. Even a slight shift, say one pound of fat for every 2-3 pounds of muscle will significantly improve gains over extended periods of training. That would be in addition to limiting the muscle mass losses while dieting.

Once again, a dose of 2.5-5 mg/day should help to keep the system running more 'normally' even at low bodyfat levels (where there is nearly no leptin signal present). This would be coupled with proper training (which is way beyond the scope of this book) and a diet that had a slight excess of both protein (1 gram+ per pound of lean body mass) and calories (10%+ over maintenance or 16-18 cal/lb is a good place to start). Adequate dietary fat is also important for optimal gains. I imagine (and hope) that most readers know the drill by this point.

Even if it doesn't eliminate fat gain completely, I'd expect bromocriptine to at least result in a more favorable ratio of muscle:fat gain during a caloric surplus and training. Regular body composition tracking (weight, skinfolds, tape measure) would be the best way to monitor gains to see if they are different with bromocriptine.

If you're a bodybuilder coming off of a drug cycle

A reality of high-level sport is drug use; we may not like it but it's the way it is. Even non-competitive athletes (especially bodybuilders) tend to use a variety of drugs in their quest for bigger, better, faster and stronger. For various reasons, far beyond the scope of this booklet, it's usually not effective to continue heavy drug use for

extended periods of time. At some point, athletes have to take a break. A very serious reality that drug-using individuals have to face is the post-cycle crash. By using high doses of drugs, normal physiology tend to get mucked up pretty severely when the drugs are finally discontinued.

While some athletes have 'solved' this problem by simply never coming off the drugs, this isn't realistic or practical for most people. It s probably not healthy either. At some point, drug use has to stop and the consequences have to be faced. These consequences run the gamut from mild to severe, but all ultimately have to do with impaired functioning of both the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal/testicular axes. In brief, in response to large doses of exogenous hormones (exogenous means from outside the body), the body will decrease production of its own hormones. Meaning that when drugs are stopped, the body is no longer producing its normal hormones.

As discussed in Chapter 7, bromocriptine may very well help to 'reset' a dysfunctional HPA and HPG/HPT axes following a steroid cycle. For this reason, I would anticipate that using bromocriptine with other commonly used post-cycle drugs (Clomid, HCG, etc.) would be ideal in an attempt to get the system up and running again. This should help to avoid the common post-cycle rebound fat gain and muscle loss that tends to occur because of screwed up hormone levels.

Once again, a dose of 2.5-5 mg would seem appropriate and taking it in the morning would still be the most logical course of action. A question with no answer as of yet would be at what point during the cycle to begin the bromocriptine. In some ways, I could see an argument for taking the bromocriptine from day 1 of the cycle; in others I could see waiting until the last few weeks of the cycle to begin bromocriptine use (similar to how drugs such as HCG and clomid are typically used).

Without data, or empirical feedback, it'd all be sheer speculation and I leave it to readers to figure it out. On this note, I should mention that many individuals on the steroid boards have been using bromocriptine for this goal already, but are bitching severely about side-effects at doses of even 1/2-3/4 of a pill (less than 2.5 mg).

Considering that one of my test subjects, a 150 pound female, only reported minor and transient (first day or two) side-effects even at doses of 5 mg per day, I can only reach one of a few conclusions about these 'hardcore' bodybuilders.

The first, and most polite, is that they're using it wrong. For some reason, these bodybuilders seem to want to take it at bedtime, which I have already told you is

incorrect; bromocriptine should be taken in the morning. As I've stated multiple times, this minimizes the side-effects and maximizes the beneficial effects.

Tangentially, I want to mention that even standard texts (such as Goodman and Gilman's *The Pharmacological Basis of Therapeutics, 9th edition*) still suggest taking bromocriptine at night, or in divided doses. While this might be appropriate for the treatment of Parkinson's disease or acromegaly, it is simply not the ideal method of dosing for the purposes described in this booklet.

A second, and likely, cause of more major side-effects in this group has to do with the rampant polypharmacy and drug stacking that typically goes on in this group. Not content to abuse one drug at a time, bodybuilders are notorious for taking multiple drugs, with different modes of action in an attempt to optimize the system.

I'm told that some individuals seem intent on stacking bromocriptine with GHB (calling it poor-man's GH), so it's not that shocking that they are reporting rather negative effects. This type of polypharmacy probably contributed to the case-study I mentioned last chapter (71) and could conceivably contribute to other problems as well. Blaming the side-effects on bromocriptine, however, is sort of missing the point.

As the data from Chapter 8 shows, bromocriptine by itself is exceptionally safe; it may be that bromocriptine stacked with other compounds is not (again, see the case study). Readers practice polypharmacy such as this at their own risk and choice.

A final, and less polite possibility is that hardcore male bodybuilders are just a bunch of pansies. Considering the role of prolactin in promoting maternal behavior in females (74) along with the increases in estrogen and progesterone (the stereotypically 'female' hormones) following a steroid cycle, this third conclusion may not be too far off. High levels of 'female' hormones after a cycle, along with depressed testosterone levels, may be turning hardcore male bodybuilders into a bunch of wimps. Perhaps bromocriptine, in conjunction with other post-cycle drugs, can help them find their testicles again.

I should mention that there is an increasing belief on these same boards that prolactin is the root cause of gyno (i.e. bitch-tits, an overdevelopment of breast tissue in males). Like so many elements of bodybuilding lore, this is incorrect even if it sounds sciency and cutting edge. Prolactin's primary role is to promote fat storage and milk production in already existing breast fat (41). Prolactin is especially potent in this regard, stimulating fat storage in breast fat cells which have been 'primed' by

estrogen first.

But the fat cells have to be there in the first place and most lean men don't have a lot of fat cells in the chest area. Development of fatty tissue in the breast (i.e. an increase in the number of fat cells, called adipogenesis or fat-cell hyperplasia) in men is under the control of estrogen and progesterone, just as in women. This is why gyno is a common occurrence during puberty (where estrogen/progesterone levels in men can become abnormally high) and in pot smokers (smoking pot raises estrogen levels).

While high levels of prolactin may promote fat storage in the fat cells which develop, estrogen and progesterone are still the primary culprits in *initiating* the process of developing gyno. As such, the typical cocktail of anti-estrogens and/or progesterone blockers are still the best approach to avoid developing gyno from steroid use. Blocking prolactin with bromocriptine is missing the point of what's really causing the gyno.

As a final comment, to squelch potential whining from the hardcore audience, I guess I better talk about the growth hormone (GH) releasing effects of bromocriptine. As I've mentioned previously, this was one of the major reasons bodybuilders have used bromocriptine (and a number of other compounds) over the years: as a GH releaser. Unfortunately, GH has a rather undeserved reputation among bodybuilders. Even as an injectable, GH tends to be not much bang for a lot of bucks.

Injectable GH has proven effective as far as fat loss goes and helps to spare muscle loss while dieting, but has a literally non-existent effect on muscle mass (75). This is also true of injectable IGF-1, another drug with an extremely undeserved reputation (76). Research shows that the lean body mass increases that systemic GH and IGF-1 do cause turn out to be connective tissue, not contractile muscle mass (75,76). In that vein, GH/IGF-1 does have beneficial effects on connective tissue and healing and might be useful for injury treatment.

But I'm still talking about injectable GH at this point. Injecting pharmacological doses of a drug and keeping blood levels elevated for a long period of time isn't the same as increasing the body's natural levels by a little bit for an hour or two (which is what most of the GH releasers do). For those in the know, it's the difference between short-acting steroid esters (i.e. dianabol, half-life = 4.5 hours) versus long-acting steroid esters (i.e. testosterone undecanoate, half-life = 16.5 days) in terms of their effect on growth.

The first will have a minimal effect unless it is dosed multiple times throughout the day (to maintain high levels of the drug in the system) while the second will have a rather profound effect with infrequent dosing patterns. Same deal here: jacking up GH a little bit for an hour or two with drugs or amino acids is far different in terms of effect than injecting GH and maintaining high levels for extended periods. The first does jack squat, the second does slightly more than jack squat (can you tell I don't think much of GH?).

The small increase in GH output that you can get from any drug or amino acid is pretty irrelevant and has a fairly minor effect on most bodily systems. It's too small and too transient to be any different. Using bromocriptine (or other drugs for that matter) to get a slight increase in GH and then expecting major benefits falls into the category of 'wishful thinking' or 'totally delusional', both of which are categories that too many bodybuilders find themselves in.

Fine, if you can afford injectable GH at effective doses, and want to use it to complement the rest of your drug stack, be my guest. I think it's overpriced for what it does (it's best use is during dieting in my opinion), but it's your money to spend if you want to. If you think that raising GH with bromocriptine is going to be your shortcut to freaky rippedness, you're mistaken and approaching delusional. Bromocriptine has other important roles, from normalizing the system during dieting, to possibly resetting the 'tone' on various hormonal axes post-cycle. The GH increase is basically irrelevant.

Being silly for a moment

Just to round out this chapter, I want to get a little bit silly. I suppose if you happen to keep mice, rats, hamsters or pigs around as pets, and one of them is having a bodyfat problem (and feeling self-conscious and less than attractive about it), bromocriptine could be used on them too.

In the animal studies to date, bromocriptine has pretty major partitioning effects, reducing bodyfat by huge amounts rapidly, while increasing muscle mass. You'll have to read the studies yourself to figure out the proper dosing, animals aren't my job.

Except monkeys, I'll make an exception for them (there's an in-joke).

Summary

Bromocriptine can conceivably be used by a variety of different groups, depending on their needs and goals. As it turns out, the use of the bromocriptine itself really isn't that variable, the same dose and schedule pretty much should work across the board. The bigger issue is the rest of that person's lifestyle (training, diet, other drugs or supplements) in terms of what goals they are after, as well as what they can expect.

During dieting, I'd expect bromocriptine to help prevent the normal metabolic adaptations that occur: decreased fat loss, crashing hormones, muscle loss, the whole shebang. This only works when coupled with a below maintenance calorie diet and/or exercise program. The lone exception appears to be post-menopausal women who see significant fat loss without a change in diet. Oh yeah, and the animal models. If you're not an animal or post-menopausal woman, you'll have to diet/exercise to get the fat loss benefits of bromocriptine.

Diabetics can use bromocriptine to improve health and reduce diabetic complications without fat loss or a change in diet. Improvements in both glucose tolerance and insulin sensitivity also appear to occur. Lean athletes or bodybuilders should find that bromocriptine, in conjunction with proper diet and training, allow a greater proportion of muscle to be gained when calories are raised above maintenance, by improving the overall partitioning of calories away from fat and towards muscle. In the long-term, this should result in more muscle and less fat, which is what we really want.

Hardcore bodybuilders may be able to use bromocriptine as well, to help reset the 'tone' of the HPA and HPG/HPT axes at the end of a steroid cycle. Finally, if you're in the habit of keeping fat pets, bromocriptine should lean them right out but you'll have to figure out the dosing yourself.

Addendum: More feedback

Since publishing the digital version of this booklet, I've gotten a good deal of feedback by folks using bromocriptine or other dopamine agonists.

The single most commonly reported effect is a total blunting of appetite during dieting. Considering how much increased appetite contributes to diet failure, that

effect alone would make it worthwhile.

In addition, effects on fat loss and overall calorie partitioning are also being reported. While bromocriptine isn't causing fat loss at maintenance calories, even a slight deficit is causing people to lose fat, especially stubborn fat, at rapid rates. I haven't heard from anyone who has used it for muscle gains or post-cycle recovery. I've also gotten feedback from one person who used pergolide, that I'll talk about next chapter.

Chapter 10: Miscellaneous miscellany

To wrap this little booklet up, I want to do a round up of a few other topics such as where to get bromocriptine, other drugs of interest, stacking bromocriptine with other compounds, possible sexual effects of bromocriptine, and a teaser for one of my longer term projects.

So where do I get it?

The question I imagine many of you are now asking is where you can get bromocriptine. As I mentioned last chapter, bromocriptine is available from overseas pharmacies without a prescription, and I would imagine it can be had in Mexican pharmacies relatively easily.

In the US, bromocriptine is a prescription drug and you might be able to convince a doctor to write you a script if you're really good (or he's *that* type of doctor). Take this booklet, get the full references if you can, and expect the typical MD song and dance when you try to convince him why you need bromocriptine if you aren't suffering from hyperprolactinemia, Parkinson's disease, or acromegaly. Good luck.

To avoid possible legal problems (this book is for information only, remember), I leave the rest to you. Finding overseas pharmacies is fairly easy and can be done via the web for anyone with a modicum of skill. There are also entire books, newsletters and groups (mainly to help Patients With AIDS who have trouble obtaining unapproved drugs) that can be resources for finding such drugs without the hassle of going through a doctor. Simply put: if you really want to get bromocriptine, you'll have to do the rest of the work. I have the utmost faith that anyone reading this book can do so if they so choose.

Other drugs of interest

Attentive readers may have noticed a slight discrepancy between the animal and human data I presented earlier. If not, you weren't paying enough attention. In the

mouse and rat studies, the best results were obtained with a combination of a D1 and D2 agonist. In human studies, only bromocriptine (a D2 agonist with slight D1 antagonism) was used. You're probably asking the following question: why not use a D1 agonist with bromocriptine? Or why didn't the researchers try the combination to see what would happen?

It's a good question with a simple answer: there isn't a D1 agonist for humans. Actually, that's not entirely true. In looking for other compounds that might work in the same or a similar fashion as bromocriptine, I did find one D1 specific drug which also has D2 activity. It's called apomorphine. Even in the absence of direct research, I imagine that it would stack incredibly well with bromocriptine or even replace it entirely. The problem is that it's injectable only, expensive and difficult to get so it doesn't meet my criteria for a good drug. As an injectable, I don't see it as usable by anyone but the super hardcore and the price and availability makes it pretty much a write-off for everyone else. The ideal would be an oral drug similar to bromocriptine but with more specific D1 activity.

The only candidate I've found is a drug called pergolide. It's one of the newer Parkinson's treatment drugs and has both D1 and D2 receptor agonist activity. It is also more potent on a mg per mg basis. 0.75 mg of pergolide gives greater effects than 2.5 of bromocriptine. This would make it a good candidate for the purposes described in this booklet. Unfortunately, the odds of getting it legally are basically zero. It's too new so you can't order it from overseas and I doubt any but the most quackish MD's would write you a prescription, even if you gave him the best song and dance in the world. It's also expensive. Even the low dose of 0.75 mg/day, it runs about \$5 per day (compared to \$1/day for bromocriptine if you get it overseas). A drug that's expensive and hard to find doesn't meet my criteria, even if it would probably be effective. It's also not nearly as well tested as bromocriptine from a safety standpoint. I'm not saying that it's dangerous per se, just that there isn't the abundance of safety data that bromocriptine has. Make sure and read the chapter addendum for more information on pergolide.

A third and very interesting drug is cabergoline. It is similar to bromocriptine in that it has primarily D2 activity although it also has weak D1 agonist activity. It is also significantly more potent on a mg per mg basis than bromocriptine (77). Its main feature is its amazing half life. With a half-life of 69 hours, cabergoline only has to be dosed at 0.25-0.5 mg twice per week, and has residual effects at 14 days after a

single oral dose. For this reason, cabergoline's main benefit is for Parkinson's patients. Normally, they'd have to take 8-16 2.5 mg bromocriptine tablets every day to raise brain dopamine (DA) levels into the therapeutic range. That's on top of the myriad other drugs they have to take. Cabergoline allows Parkinson's patients to take a single pill twice per week. Like pergolide, cabergoline is new, hard to get, and expensive (even at a twice per week dosing, it'll easily run you twice as much as bromocriptine).

A final drug of interest that many of you may be thinking about is the prescription amino acid L-dopa. Like bromocriptine, L-dopa has been used by bodybuilders as a GH releaser since the 80's. It's also used in Parkinson's patients as an adjunct to the other drugs as L-dopa is a precursor to DA in the brain. It's relatively easily available, and a natural source (called *Mucuna Pruriens* or velvet beans) has been advertised in bodybuilding magazines recently and marketed as a GH releaser.

I should note that brain DA can also be raised, at least for short periods, with high doses of the amino acid L-tyrosine, which also converts to DA. That same L-tyrosine will also convert to adrenaline and noradrenaline (epinephrine and norepinephrine) and I've had athletes use it as a pre-event stimulant for that very reason. One to three grams of L-tyrosine with 200 mg of caffeine, taken an hour before an event, is as effective as the ephedrine/caffeine stack at improving performance, but it's not banned. Finally, nicotine appears to raise DA, which may be part of both its behavioral and metabolic effects.

The problem I have with using L-dopa, L-tyrosine or related compounds in this fashion (chronic high dosing as opposed to single dosing for performance enhancement) is that one hypothesis of the neurodegeneration that *causes* Parkinson's disease is the free-radical oxidation of DA (78). That is, maintaining high levels of DA, especially in the face of the oxidative stress that we undergo on a daily basis may be a cause of the damage to the DA-producing neurons because of free radical damage. It is this damage to DA-producing neurons that can eventually cause Parkinson's to develop.

In contrast, it has been suggested, but not proven, that DA agonists such as bromocriptine may actually be neuroprotective and decrease the amount of damage which occurs to DA-producing neurons (79,80). That is, raising DA chronically may damage dopaminergic neurons from auto-oxidation of the DA; DA agonists, which

activate the DA receptors without raising DA may protect those same neurons.

For this reason, I think that trying to keep DA levels elevated with such substances (L-dopa, L-tyrosine, nicotine) carries an unnecessary risk. Even if it is slight, the consequences (Parkinson's disease later in life) are monstrous. As per the foreword, these compounds don't meet my requirement of safe, even if they are cheap and readily available. Being a little more ripped or muscular now isn't worth the potential long-term consequences.

Stacking bromocriptine with other diet drugs

Although research into dieting and obesity-treatment drugs has been going on for decades, none of the drugs developed have been more than minimally successful. One of the biggest problems is that the drugs eventually quit working and weight loss stops. Usually a 5-10% weight loss is accomplished but no more. Additionally, when the drug is discontinued the body puts the fat right back on, frequently with more to spare. A long-held question has always been why this was happening. Was the brain adapting, were other systems kicking in to compensate, or was it something else entirely? It looks like the body was simply adapting and that the adaptation is related to the leptin system, yet again. Are we really surprised at this point?

Remember that leptin levels drop in response to decreasing bodyfat levels which is what 'tells' the brain what's going on. So as obesity drugs cause fat loss (through mechanisms from appetite suppression to increased caloric expenditure), leptin levels go down. As the model I presented would predict, the body adapts to that falling leptin in the same way as it would to dieting or exercise: by slowing metabolic rate, fat burning, etc. The fact that it's a drug causing the fat loss is irrelevant. Fat loss equals lower leptin which ultimately equals adaptation as the brain 'senses' what's going on. This raises a fairly logical question: if bromocriptine is replacing leptin signaling under other conditions, could it keep other diet drugs working longer?

Although not yet tested directly, a fairly recent study suggests that it may. In this study, low-dose leptin was given to rats who were also given the dieting drug Sibutramine (trade name: Meridia) to see if it would prevent the normal adaptation to weight loss (81). Meridia is one of the newer appetite suppressants, which works by inhibiting the uptake of serotonin and noradrenaline (two of the other main

neurotransmitters in the brain).

The study found that maintaining leptin at normal levels via injection during fat loss (from the Meridia) prevented the rats from adapting metabolically. None of the metabolic adaptations normally associated with fat loss and dropping leptin occurred and weight loss continued without a plateau (the control, leptin only, and sibutramine only groups plateaued early). This suggests that dropping leptin is what's causing most dieting drugs to quit working over time. In that bromocriptine is 'replacing' leptin in the brain, it would seem that bromocriptine might also improve the effects of other diet drugs.

Unfortunately, because of its mechanism Meridia may be one of the few dieting compounds that bromocriptine can be stacked with in this fashion. I suspect that they would stack amazingly well in humans: bromocriptine or another DA agonist would be maintaining DA levels, while Meridia would be helping to maintain serotonin and noradrenaline levels. As mentioned last chapter, beta-agonist compounds such as the EC stack or clenbuterol actually block the effects of bromocriptine. Once again, since bromocriptine should make the EC stack unnecessary in the first place, this isn't any really big deal (unless you just like being wired all the time, like I do).

In any event, I want to mention that combining drugs in this fashion, when the combination is untested should be practiced with the utmost of caution. Any time you combine drugs in this way, the possibility of a negative interaction or more serious side-effects becomes more likely. You do so at your own risk.

Bromocriptine and sex

Ok, I bet that topic heading grabbed your attention, even if you're wondering what sex has to do with any of this. But let's face it, most of us want to be more muscular and/or leaner for the most superficial and shallow of reasons. Sure, we tell people that it's to be healthier or live a fuller life, or to fulfill some psychological void in our life, and there may be a little truth to all of that. In the big scheme of things, it's pretty much bull. We mostly put ourselves through this to look better naked. Or to look good enough to potential sexual partners so that we get more of an opportunity to frolic naked with them.

In that vein, I should mention that bromocriptine may have pro-sexual effects on

top of everything else. Just as it is involved in so many other aspects of human physiology, the dopaminergic (DA producing) system is involved in sexual response. Dopamine appears to be involved in both sexual response and male erection, although it's role in female sexual response is less well established (82).

A known response to dieting is a decrease in both sexual interest and ability, which makes a certain type of evolutionary sense. When you're starving really isn't a great time to get your mate pregnant because there won't be enough food available to bring the baby to term. Dropping leptin, and its effects on DA (and subsequently other hormones such as testosterone and estrogen, both of which are involved in sex drive) might well be involved in this decrease in sexual function (it's already established that dropping leptin shuts down normal female reproductive functioning). Bromocriptine, by normalizing DA levels might be expected to have pro-sexual effects in this regard.

Additionally, a surge in prolactin following orgasm appears to be related to the refractory period that tends to occur. I also have to wonder, considering its role in promoting maternal/caring behavior, if this surge in prolactin is related to some of the bonding that goes on between men and women, women especially, when they have sex.

In any event, lowering prolactin with bromocriptine might allow a shorter refractory period by blunting the normal increase after orgasm. That's on top of potentially maintaining normal sexual function as men and women diet to extremely low bodyfat percentages. I eagerly await feedback from readers on this topic. Pictures (JPEGs please) and/or video tapes would also be nice. My email and snail mail addresses are in the front of the book, please put any submissions in a plain brown wrapper.

A teaser for an upcoming project: killing fat cells

In past chapters, I made oblique reference to the fact that bromocriptine may be able to actually get rid of fat cells (a process referred to as apoptosis, or cell death) permanently. To get everybody hot and bothered, I wanted to tell you a little about that. First, what is apoptosis?

Under a certain set of conditions, all cells can enter what is termed the 'death program', (which would be a great name for a rock band). In this vein, there are also

death genes and death receptors on cells, which is altogether too cool. Once initiated, the death program can't be aborted and the cell will die.

Basically, once the death program starts, the mitochondria more or less explodes, causing the cell to collapse upon itself and basically self-destruct, releasing its contents into circulation. Macrophages, which are specialized cellular critters that deal with cellular junk, sweep in to get rid of the debris. While apoptosis was known to occur in most other cells in the body, it was only fairly recently that apoptosis of fat cells was observed.

This was part of the initial evidence suggesting that bromocriptine and leptin were working through similar pathways (59), and what led me to examine bromocriptine in the first place. It was known already that injecting leptin into the bloodstream of a lean rat causes fat cells to be deleted (i.e. undergo apoptosis). It was then found that injecting leptin into the brain of a lean rat caused fat cell deletion too (57), and that bromocriptine administration caused the same effect (48). This was a bit curious as it suggested that some central effect (i.e. signal from the brain to the fat cells) was causing the fat cells to die, instead of a direct effect of leptin on the fat cell. In any event, all of this leads to the fact that fat cells can be gotten rid of, at least in lean mice.

But what about humans? In the past, it was always thought that once you had fat cells, they were yours forever, short of liposuction. The standard dogma, which I mistakenly believed for years, was that you could shrink fat cells, but you couldn't ever get rid of them. New data suggests that this isn't the case. You can both increase and decrease fat cell number, under the right conditions. Unfortunately, increasing fat cell number is a lot easier than decreasing fat cell number.

Apoptosis of fat cells does happen in humans, although it generally only occurs under severe conditions such as cancer wasting (84). HIV protease inhibitors appear to cause a site-specific deletion of fat cells (85), where fat cells on the torso are lost and redistributed to the neck, forming a characteristic hump.

All of this says that fat cells can be killed in living humans. The question is whether or not it can be done safely and effectively or without such extreme conditions as cancer or HIV drugs. My apoptosis project is ongoing and I hope to have recommendations on how to do it within the next year. It will most likely include getting below a certain level of leanness as only fat-depleted fat cells are eligible to undergo apoptosis in the first place. Probably 10% bodyfat for males and 18% for

females or so would be required.

The next step would be using a specific combination of nutrients, exercise, and even drugs to get the death program rolling. It may very well require site injection of the compounds that appear to trigger the death program in the first place. The key is raising the right chemicals at the right time for long enough to start the death program, without harming the rest of the body. This is not a trivial process which is why I'm not giving you any ideas right now.

At this point, doing it isn't the problem so much as making sure it doesn't kill the person. Site injection of certain chemical compounds (such as TNF- α or certain prostaglandins) would get the death program rolling, but at a high cost to the rest of the body. Killing fat cells also causes a lot of cellular debris to be dumped into the body. This can cause a host of problems from autoimmune reactions to systemic Lupus or even worse (86).

The first problem I have to solve is how to trigger the death program in the first place. The second and more important problem I have to deal with is how to control the process so that too much stuff doesn't get dumped into the bloodstream. Under one scenario, this could cause an autoimmune reaction. Under another, I could see much graver possibilities such as stroke or heart attack because too much cellular debris got lodged in a blood vessel and blocked it off.

Since I generally find that killing readers is bad for repeat business, I leave the idea of fat cell killing as a teaser until I figure if it can be done safely, or at all. Since I'll be the first guinea pig for this, I'll figure it out or die trying.

Addendum: Feedback on Pergolide

Since writing this booklet, I've gotten feedback from exactly one person who was able to obtain pergolide from his doctor. He was nice enough to give me extensive feedback on the drug, although he asked to remain anonymous. As I mentioned above, as a combination D1/D2 agonist, I'd expect pergolide to be far more effective than bromocriptine or the other D2 agonist only drugs.

His first observation and the one I really want to make a point of is the potency. Even a low dose of 1 mg put him on his ass, literally knocked him out. This makes the 0.75 mg I listed above as being a ridiculously high starting dose. He actually had

to start with a dose of 0.05 mg and build up from there. He described building up to a rather high dose of 4 mg over a period of many many months, increasing dose by a mere 0.05-0.125 mg every week to 10 days. With each increase, he noted a return of side-effects. He also mentioned that his diet the day *prior* to raising the dose had a huge impact on his ability to tolerate the higher dose. If he had eaten well, was relatively well carbed-up, etc. the dosage increase was well tolerated with fairly minor side-effects. If not, well...

He also mentioned some rather potent behavioral effects with increasing doses. He described a few different effects. The first was being in an almost dream state when he would increase the dose. Not quite to the point of hallucination but close. He simply had to be aware to stay out of certain situations to avoid getting himself into trouble because his judgement was sometimes impaired. The second effect was an almost hyper-sensitivity to other people, bordering on paranoia but not exactly. Rather, he could read people better, and could tell when they were having negative thoughts about him.

I suspect these effects have to do with the ergot derivative nature of these types of drugs. The first effect, the dream-state, would tie right into an ergotamine type of effect. The second effect was probably just him more aware of the otherwise subconscious signals (i.e. body-language, tone of voice) that the people were giving off towards him. He never noted true paranoia, the kind where you think everyone is out to get you, or where you're hallucinating plots against you. Rather, the folks he got negative vibes off of invariably did have negative intentions towards him. For whatever reason, he could simply read people better with the drug in his system.

Finally, he reported the partitioning effects to me, which can only be described as profound. He found that, even at a relatively low bodyweight, he was almost unable to gain fat even with massive caloric intakes (and those calories from junk food). It took raising calories to absurdly high levels (10,000 calories per day of junk food) for fat gain to become apparent. Rather, the excess calories were either burned off or moved towards muscle tissue. He also mentioned an incidence where he raised the dose but was very lax about eating enough and reported bodyfat levels literally dropping by what appeared to be several percentage points almost instantly.

His next experiment will be to obtain a prescription for Meridia (or another drug/combo of drugs that modulate serotonin and noradrenaline) to see if the combination has even more profound effects.

To state it again, he really wanted me to make readers aware of the *extreme* potency of pergolide. Milligram for milligram, pergolide appears to be at least 10 times as potent as bromocriptine and perhaps even more than that. Any reader who decides to experiment with pergolide must take as many precautions as possible, and be as conservative as possible in terms of both daily dosing and increasing dosage.

Appendix 1: The FDA and bromocriptine

In 1998, a company called Ergo Science submitted an application to the FDA to allow Ergoset (tm), a fast acting form of bromociprine, to be marketed and used for the treatment of diabetes. While the application was turned down, I want to discuss the proceedings for completeness.

As a quick note, I want to mention that all of the data and quotes is coming out of the same reference source: the FDA transcript of the application proceedings (66). To keep things simple, I'm only going to indicate the specific pages that the data or quotes are coming from, without continuing to put the reference number in parentheses. This is just for space saving. On the rare occasion that I use another reference, I'll indicate it by number.

Introduction

Recall from previous chapters that bromocriptine has been around, and used for multiple purposes (hyperprolactinemia, Parkinson's disease, acromegaly), for nearly 30 years. In that context, the FDA application that was filed had to do with marketing bromocriptine, in this case a specifically fast-acting form called Ergoset (tm), for a new use: the treatment of Type II diabetes.

Basically, this wasn't a case where an application for new drug approval was being sought: it was a case of a pre-existing drug (in a slightly different form) being used for a new purpose.

It would be a vast understatement to say that obtaining FDA approval, especially in today's climate, involves jumping through hoop after hoop after hoop. Clinical trials have to be performed, safety and risk data has to be tallied and submitted all before the FDA application can be submitted. The full process involves years of research and millions of dollars.

Of course, all of the money and time investment is worth it if a company comes up with a new drug to treat a severe disease; the revenue for such a drug can be in the billions (think Viagra) if it all works out. It can also mean bankruptcy if the process

doesn't work out. Large drug companies frequently lose millions on the development of drugs which don't pass FDA muster but make it up when they get that one big hit of a drug that does work. Smaller companies, without the necessary capital, are at a huge disadvantage in this regard. They literally have to put all their eggs in one basket and if the drug application is denied, odds are the company will fold.

Even then, the FDA doesn't appear to be terribly consistent when it comes to approval. In theory, the FDA compares the benefit:risk profile (that is, does the drug generate enough of a benefit, with a low enough risk) to decide if a drug can or should be marketed for a given purpose. In reality, it's not that simple.

Some drugs (such as Phen/Fen) can be fast-tracked, meaning that the FDA lets them slide through some of the more tedious parts of the drug application process to get the drug to market quickly (this is usually done when a drug is expected to offer such incredible benefits that its worth rushing to market).

This comes with risks, as the Phen/Fen debacle pointed out; the combination was effective for obesity treatment but was also linked to an increase in heart-valve defects (noting again, that obese individuals, are notorious for having preexisting problems). It was pulled off the market for this reason although there is some debate as to whether the drug was causing the problems in the first place (this is similar to what happened with bromocriptine and stopping lactation).

Some pundits have pointed out that, if it were put up for FDA approval today, aspirin would not get approval because it doesn't have a good enough benefit:risk profile. The point I'm trying to make is that FDA approval can frequently be as much about luck and money as reality. I hate to contribute to FDA-drug monopoly conspiracy theories but it's interesting that drugs with major corporate/financial backing seem to get FDA approval more easily than drugs from smaller companies. I'm sure that this is a mere coincidence.

I guess my point, if I had to make one, is that FDA approval doesn't mean a compound is necessarily 'safe' or effective (as was the case of Phen/Fen, or thalidomide which I mentioned previously) anymore than not getting FDA approval means that it's unsafe or ineffective. It means that, for whatever reasons, the FDA didn't approve that drug's use for that specific purpose.

Diabetes, bromocriptine and the FDA

Although the term epidemic seems a bit over the top, in the case of Type II diabetes it's not far off. Between 1991 and 2000, Type II diabetes increased by 49%, and that's not even including the folks who are merely insulin resistance (or pre-diabetic). Upwards of 25% of children (noting that Type II used to be called Adult onset diabetes) children under age 10 and 21% between 11 and 18 are showing pre-diabetic problems (impaired glucose tolerance and all of the rest) as well (87). It should be fairly clear that any novel treatment for this disease that is both safe and effective would be a huge blessing. On top of making the company that held the use patent about a zillion dollars.

In 1998, the company Ergo Science (<http://www.ergo.com>) applied for FDA approval to market bromocriptine for the treatment of Type II diabetes. I also want to mention that Ergo Science did not apply to the FDA to use bromocriptine for the treatment of obesity or fat loss (as one internet writer has incorrectly suggested). Ergo Science was only applying for approval to market Ergoset (tm) for the treatment of Type II diabetes, nothing else.

I also want to mention that Ergo Science actually brought a novel form of bromocriptine, called Ergoset (tm) in for FDA approval; it's also what was used in the diabetic studies. Ergoset (tm) differs from standard bromocriptine (i.e. what you could get overseas or from a willing physician) only in how quickly it gets into the system (pg. 203). Ergoset (tm) peaks in the blood faster than parlodel/bromocriptine but that's the only major difference; the effects are the same.

Now, they used this novel form of bromocriptine, so that they could get exclusivity to sell it. This has to do with the finances involved in bringing a drug to market. When new drugs are introduced, the company producing it is given some period of time where they have exclusivity to market and sell it without any generics being offered by other companies. This gives that company time to make back the money that they invested in testing the drug, without another company being able to profit. This is also a main reason why there tends to be a lack of real research into non-drug solutions (i.e. using vitamins or other nutrients) by major drug companies for various diseases; since those compounds can't be patented, nobody stands to get exclusivity rights. So nobody is going to spend the money to do the studies if they can't get an exclusivity patent.

The exclusivity patent on bromocriptine expired years ago, so there's no money in using it in that form. So Ergo Science had to come up with a slightly different form: Ergoset (tm). Again, the only difference between Ergoset (tm) is one of rate of entry into the bloodstream; Ergoset (tm) gets there a little bit faster. Other than that, it's identical to generic parlodel/bromocriptine mesylate meaning that the data on one is applicable to the data on the other.

In any event, in presenting their case to the FDA, Ergo Science basically had to provide evidence concerning a number of factors, related to the effectiveness, safety, and mechanisms behind the drug's effects. In brief, and trying to avoid more yammering about FDA/drug company conspiracies, they had to convince the FDA that the drug has a sufficient effectiveness:risk ratio. If so, the FDA will give approval to market the drug for that purpose; if not, it won't. Fundamentally, that's the bottom line.

The peanut gallery

Although I don't want to go into huge details about all the folks involved in the FDA proceedings, I did want to make a few comments about them. Basically, both Ergo Science and the FDA brought their crew of folks to discuss the issue. I see it exactly like a gang fight in any run down neighborhood, but nerdier. Substitute 9mm semi-automatics with slide rules and colored bandanas with safety goggles and lab coats and you've got the rough idea.

Ergo Science had many of the primary researchers from the studies, their statistician, a cardiac specialist, etc. on their squad; the FDA had a bunch of MD and PhD types who were going to examine the data. There was a great deal of flowery language as it went on (again, I suggest readers read the actual transcript if they are interested and/or need sleep-inducing material) as tends to happen when everybody has a bunch of letters after their names. There was also a lot of interrupting and generally poor speaking on behalf of everybody; it sounded about like a high-school debate in some ways. And the transcription was really bad.

Frankly, both groups had some severe failings in my opinion. The Ergo Science crew came fairly well prepared but were lacking some of the data that they should have had (stuff they either didn't measure in their experiments or simply didn't bring with them). This didn't do much to help their case, because the FDA folks spent

bring with them). This didn't do much to help their case, because the FDA folks spent a lot of time nitpicking about little details that the Ergo Science crew didn't have the answers to. Ergo Science could have been better prepared as far as I was concerned (of course, this is easy for me to say 4 years after the fact).

On the FDA side, well, they had some pretty choice folks on their committee. Yes, I'm being sarcastic. I had three (and a half) basic problems with the FDA crew in terms of the overall proceedings. All three problems basically come down to the FDA crew being dumb as dirt but I want to be more specific.

First, and considering that they were sitting on the approval committee for a diabetic drug, it was amazing that at least one of the committee members had no clue about a rather standard technique in research studies, namely the glucose/insulin clamp technique (pg 63). The clamp technique refers to a method by which blood glucose and/or insulin are kept constant (i.e. 'clamped') during the study, so that you can figure out what's going on.

That is, normally if blood glucose changes, so does insulin; and, vice versa. Clamping down one lets you change the other and see what is happening. Because, if both are changing at the same time, it's impossible to draw any meaningful conclusions about what's doing what. This is one of the most common techniques used in diabetic research, to check for changes in insulin sensitivity and glucose disposal, and having someone on the FDA side totally unfamiliar with the technique seems silly; how can he possibly evaluate the data on a technique he doesn't understand?

A second and related issue was the FDA folk's utter cluelessness about body composition measurement and body density. Once again, when you look at changes in body composition, measuring body density (via various methods from underwater weighing to electrical impedance to calipers, all of which estimate body density) is standard stuff. Several of the FDA folks couldn't quite wrap their brains around the concept, making me question their ability to judge the data in any meaningful way (see pg. 140, for example).

Finally, and perhaps most annoyingly, the FDA folks just couldn't get past the changes in prolactin in looking at the results. That is, as I mentioned in an earlier chapter, the primary observation from the earliest studies on bromocriptine had to do with changes in prolactin. While it was eventually found that the effects of bromocriptine were not being mediated through changes in prolactin, the FDA guys

just kept harping on it for some reason; they just couldn't get it through their thick skulls that the drop in prolactin was not responsible for any of the other changes (see, for example, pg 198-200).

Along with that, they kept trying to suggest that maybe bromocriptine was having effects in the body that weren't being mediated through the brain (i.e. via changes in prolactin or peripheral effects of bromocriptine) despite numerous assurances by the Ergo Science crew that not only was it not the case, it could not be the case (pg. 204-206). I don't know if the FDA guys weren't listening or were just looking for an excuse to turn it down, but they were being dense in any case.

To restate it, bromocriptine works centrally (in the brain) by altering a number of neurotransmitter levels, and the major metabolic effects occur irrespective of changes in prolactin. Again, that's easy for me to say, 4 years later, with a handful more data available to me. Even with the data available at the time, it was pretty clear that's how bromocriptine was working; the FDA just couldn't see it.

I'm not going to run through the entire case that Ergo Science presented to the FDA in detail, since it would mean repeating most of what's in this book. If you want to see how and what they presented, read it for yourself. Basically, their presentation fell into a few categories: beneficial effects, safety/risk data, and mechanisms of action. I'll address each in turn.

Effectiveness

Although I presented the data on diabetics fairly briefly, there was a good bit more to it and there was a lot of discussion in the FDA proceedings about the effects, in addition to a lot of nitpicking. One of the problems with the Ergoset (tm)/diabetic studies was the length. The formal studies were only 16 to 24 weeks long, but were typically extended out to 72 weeks or so, but without a placebo control group. The FDA seems to consider data less than a year suspect, both in terms of effectiveness and safety. Simply, the Ergo Science studies weren't long enough to really make the FDA happy (pg. 227-228).

A second issue had to do with the changes in HbA1c (glycosylated hemoglobin) that occurred in the studies. HbA1c refers to hemoglobin that has become glycosylated (had glucose attached to it) and is simply one of the major

become glycosylated (had glucose attached to it) and is simply one of the major markers of diabetic complications used in studies of this nature.

Although I described that HbA1c went down in the studies in a previous chapter, I didn't go into a lot of detail or specifics. It turns out that, in the Ergoset (tm) group, after the initial drop, HbA1c started to rise again returning more or less towards baseline by the end of the study (see Fig 1. below). At the same time, the HbA1c of the placebo saw an initial improvement and then worsened throughout the study.

Now this has to be taken within the context that most diabetics, left untreated, will show the same type of deterioration (i.e. increase) in HbA1c anyhow; it's a consequence of the disease. Even at the end of the study, back at baseline, the bromocriptine group was still better off than the placebo group (which had seen no improvement at all, and got much worse) (see ref. 40, pg. 1158 or Figure 1 below). If you're wondering about the initial drop in HbA1c in the placebo group, it probably has to do with the fact that most people change their habits (in this case, dietary) when they start a new study protocol. Once again, after that initial drop, as the graph shows, the placebo group worsened fairly rapidly over the length of the study. At the end of the study, the Ergoset (tm) group had lost ground but were still better off than the placebo group.

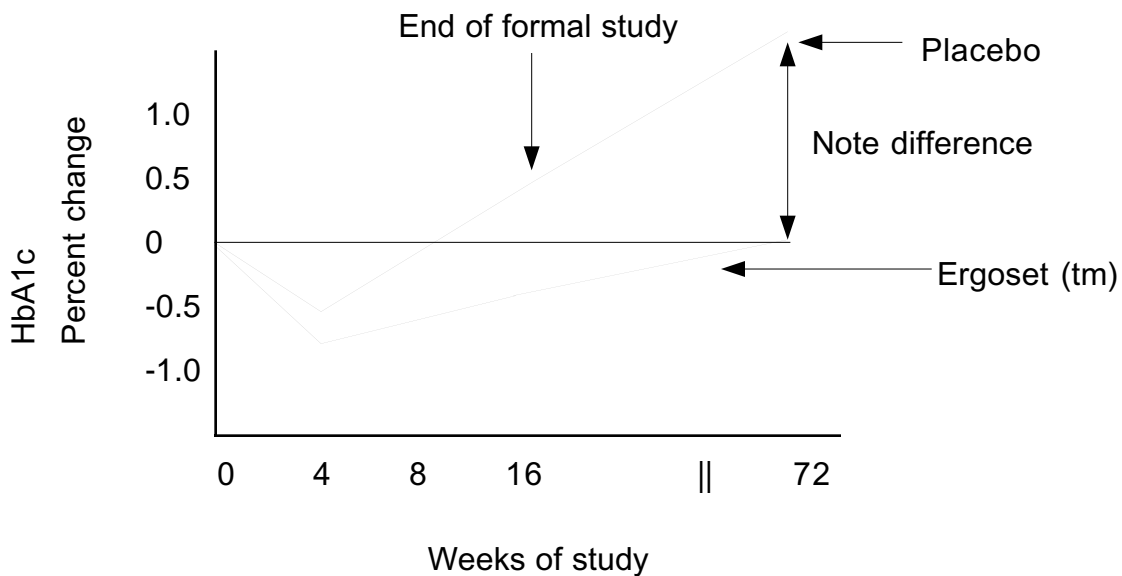
At this point, the studies were extended, but the placebo group was discontinued and this caused a problem. Over the full length of the extension, levels of HbA1c kept getting worse even in the treatment group (once again, this is 100% typical with diabetes anyhow; it's a progressive disease). Unfortunately, without a placebo group, there was no way to tell if the bromocriptine group was still better off than folks given no drug. It was suggested that it was most likely the case that they were, but the FDA won't really deal with 'suggestions'; they wanted data and the Ergo Science crew simply didn't have it.

As the graph shows, at all time points, the bromocriptine group was still better off overall, as a lower HbA1c level means less diabetic complications over time, which is one of the major end criteria for such drugs. Dealing with Type II diabetes is mainly a matter of minimizing the health consequences that occur if the disease is left untreated; they're not looking for a cure per se. That is, bromocriptine was still effective in comparison to no drug at all.

The main point of the graph is that even though the Ergoset (tm) group worsened, and returned to baseline at 72 weeks, they would still be expected to be

better off than the untreated group overall. The extension on the placebo group is what would be 'assumed' to happen based on the previous trend, it was not measured directly. Because of the difference, the relative risk of diabetic complications would be expected to be much less in the bromocriptine group (it was estimated to be 35-37% less based on the decrease in HbA1c levels).

Figure 1: Changes in HbA1c



The next issue regarding effectiveness had to do with the absolute improvement in Hb1AC with Ergoset (tm). According to their own guidelines, the FDA typically won't consider a drug that decreases Hb1AC less than 1% to be effective enough to warrant approval. Although 30% of the subjects did achieve greater than a 1% reduction, the average drop in Hb1AC by approximately 0.7% which didn't make the cutoff (pg. 161). However, it's clear that this isn't an absolute cutoff, as the FDA did approve the drug acarbose (which slows the digestion of carbohydrates in the stomach so that blood glucose is better controlled) although it only decreased Hb1AC by 0.76%.

The FDA defended their stance by arguing "...the reason in the case of acarbose we accepted -0.76 since this was really a drug the effect of which was non-

systemic, so our risk benefit became a little bit more defined in favor of the drug, despite a relatively modest -0.76." (pg. 168) Basically they made an exception for this one drug, primarily because its mechanism was not systemic (it worked in the stomach and the stomach alone) and they had no concerns over safety.

They also mention "...that we can approve a drug that has an effect of .1 hemoglobin [Hb1AC] units if the benefit is justified by the risk. If it has negligible risk and yet you can show that kind of magnitude then you might -- you know, it seems highly unlikely, but you could approve such a drug." (pg. 168) That is, the FDA guidelines are really up to their own individual interpretation and there are no hard and fast rules to any of it. This is great for the FDA, since they can change their rules to suit the situation; and crappy for drug companies who don't know what standard they will be held to.

Another issue that the FDA crew had with Ergo Science had to do with changes in triglyceride levels. As I told you earlier, blood triglyceride levels typically go up to extreme levels in insulin resistance/diabetes (because insulin can't drive them into fat cells where they belong). Research is finding that blood triglyceride levels are an independent risk factor for heart disease, so changes in blood levels are important from a health and diabetic complication standpoint.

The basic issue that the FDA had was the the Ergoset (tm) trials showed only a modest improvement on blood triglyceride levels in the first place (pg. 235) and there was the same question about long-term effects as there was with the Hb1AC data I described above (i.e. do blood triglyceride levels stay down with long-term use). Basically, it seems unlikely the Ergoset (tm) by itself is sufficient to fix *all* of the metabolic defects seen in Type II diabetes (which makes sense as diabetes is a multi-factorial disease involving a large number of different defects), even if it does improve many of them.

Considering the nature of diabetes, and the fact that treatment commonly involves multiple drugs and/or diet and exercise modification, this is no big surprise. Even working centrally, a drug such as Ergoset (tm) can only do so much, especially in the absence of weight loss and dietary changes (note that weight was deliberately maintained meaning that the diabetic subjects were on the same shitty diet that made them diabetic in the first place).

As a final issue in terms of effectiveness, the FDA took some issue with the population group (in terms of ethnic background) that were used in the Ergoset (tm)

trials. Since the studies were performed in San Antonio, there was a definite skewing of ethnicities, and the FDA didn't feel that all ethnic groups were adequately represented. This is important as it's becoming clear that there are significant ethnic differences in the rate of development of Type II diabetes.

Studies indicate that 13% of African-Americans, 10.2% of Hispanics, yet only 6.5% of whites develop Type II diabetes so it's important to show that any new drug will be effective in the population groups that are at the highest risk. The Ergoset (tm) trials didn't do that very well (pg. 234-235). As with some of the earlier data, this was simply a mistake on the part of Ergo Science; they should have made sure to include a wider sample of ethnicities in their trials in preparation to take their data to the FDA.

An issue related to this was that some study subjects were incredibly good responders, showing large scale results quickly, while others were not. Ultimately, this is no big surprise; for any drug you can name, some people will respond better and/or faster than others (pg. 243). Something that the FDA wanted Ergo Science to study was whether or not you could tell who would be a rapid/good responder and who wouldn't be (this would have implications for who would ideally be suited for bromocriptine treatment). That data, of course, wasn't available at the time.

In regard to this, the FDA stated:

"I think the data suggestion that some patients respond better than others is applicable for any drug, and one thing that I think could be done is to look at the good responders and the poor responders, particularly since we now know it's metabolized by the cytochrome P3A4 system. Will the patients who are good responders on drugs that are known to go through that system, for example, or are there mutations in that that have been shown to affect metabolism of the drugs?" (pg. 242)

Safety/risk data

The safety/risk data was basically what I presented in Chapter 8. On top of the endless data on bromocriptine in hyperprolactinemia and other diseases, the data on Ergoset (tm) in diabetics included all the data I already gave you.

The basic issue that the FDA had in terms of the safety data had to do with the length of the studies. Short-term studies can only tell researchers a limited amount

about the potential long-term effects of a drug in terms of possible negatives. As described above, the longest Ergoset (tm) trials only stretched to 72 weeks, and the FDA wanted data of a year or more to be sure that both the effects would be maintained, as well as being more clear on the safety issues (pg. 227-228).

There is also the issue of very limited data in terms of drug-drug interactions that can occur. Considering that Type II diabetics are frequently put on multiple drugs to control their disease, it's crucial to know that there won't be negative interactions when a new drug is added to the mixture. Giving a novel drug that makes the problem worse because of a negative interaction isn't something the FDA wants to do. This really isn't a huge deal for the primary uses of bromocriptine discussed in this booklet, since bromocriptine is the only drug we're dealing with.

Overall, however, the FDA didn't really make too big of an issue over the limited number of negative occurrences that I described back in Chapter 8. When working with Type II diabetics, with severely pre-existing pathologies, certain problems are expected to occur. Since bromocriptine wasn't causally implicated in any of the major events (2 liver problems, 12 myocardial infarcts), this wasn't a major issue and the FDA didn't make it one.

The FDA did, however, want more safety data overall, as well as longer-term safety data. With a few more studies, in larger populations with a greater variety of ethnicities, it's likely that these criticisms would have disappeared.

Mechanisms

The final area of contention by the FDA had to do with the proposed mechanism of action of Ergoset (tm) in correcting the metabolic defects involved in Type II diabetes. At the time of the application (1998) much of the data I gave you in previous chapters was simply not available. There was a limited amount of data in animals, but very little in humans in terms of the neurobiology and neurochemistry involved in the mechanism behind bromocriptine.

For a variety of reasons, the FDA likes to know what the actual mechanisms of the drug are. There is some sense to this, knowing the exact action allows better prediction of possible interactions with other drugs. Considering that most diabetics are put on multiple drugs to control the disease, knowing the mechanism of action of

bromocriptine ties in with the overall safety/risk profile; it allows you to make some vague predictions about possible negative interactions.

Unfortunately, the FDA didn't seem to want to accept animal data only, in terms of neurochemical changes that bromocriptine has shown to cause (refer to previous chapters if you've forgotten it already). More unfortunately, since it's ethically more or less impossible to biopsy human brains to measure changes in neurochemicals, you end up with sort of a Catch-22 situation. You can't measure the levels of brain chemicals directly in humans, the FDA won't take animal data, and using indirect measures won't let you know for certain that the effects are occurring at the brain in the first place (pg. 236-237 for example).

As I mentioned above, the FDA really seemed to have a problem wrapping their little FDA brains around the idea that bromocriptine was working centrally, in the brain. They fixated on the changes in prolactin, despite numerous assurances that those changes were absolutely not responsible for the observed effects. Unfortunately, since Ergo Science either forgot (or was too lazy) to bring data on other hormonal changes, such as cortisol, glucagon and the catecholamines, prolactin was about all that they had to present (see pg 206-210 for example). Data on other biochemical changes (unrelated to prolactin) would have gone a long way in helping Ergo Science make their case.

There was also some concern that some of the observed changes in the studies might be mediated by effects unrelated to the drug itself (pg. 237). That is, even small changes in food intake, activity, etc. can significantly affect diabetic parameters and the studies simply could not be controlled to that level. Considering that even the placebo group saw initial improvement in Hb1AC, it seems possible that there were confounds to the overall results.

The bottom line

When it came down to it, the FDA asked 4 primary questions, polling their committee members to vote yes or no in favor of approving Ergoset (tm) for the treatment of Type II diabetes.

The first question was "Are the study designs adequate to assess the efficacy and safety of the is drug for the proposed patient population?" (pg. 237). Basically,

and safety of the is drug for the proposed patient population?" (pg. 237). Basically, was the study data sufficient to allow the drug to be marketed across the board for Type II diabetics? The entire committee voted no to this question; they didn't feel that the limited research, with limitations in terms of length, and both gender and ethnicity distribution made a sufficient case in favor of Ergoset (tm).

The second question was "What is the clinical significance of the reduced hemoglobin A1c levels observed in the pivotal studies?" (pg. 239). Without going into details of individual answers (read it yourself), there were 2 answers of no, 3 answers of yes, 4 answers of maybe (a conditional yes), and one undecided. Basically, there were trends in the right direction, given the limitations of the studies, but not quite enough to overwhelm the committee.

The third question was "What is the appropriate role of the prospectively defined responder analysis in the evaluation and/or labeling of this therapy?" (pg. 240). That is, considering the variance in responders versus non-responders, is there any way to market the drug towards the patients most likely to benefit from it. The committee members weren't very good in giving yes or no answers so I'm going to cop out and not count it up for you. Go read the transcript if you want to wade through it. Basically, as with question 1, they saw the trend in the data, thought it was interesting, but wanted a little bit more data before they could vote yes completely.

The final question was "Based on the efficacy and safety data presented, and your assessment of the overall benefits compared to the risks of bromocriptine therapy, do you recommend that this drug be approved for use in the proposed patient population?" (pg. 244). This is really the pivotal question, did the FDA think that the data presented by Ergo Science made the case for Ergoset (tm) to be used in this population. The committee voted no unanimously. And the drug was turned down.

Final comments

In closing out this chapter and the booklet, I want to make a few final comments. Despite some blathering on the internet to the contrary, the FDA didn't turn down Ergoset (tm), a novel form of bromocriptine, because it wasn't effective or was dangerous. There simply wasn't sufficient data, in terms of overall effectiveness, different population subgroups, or the mechanisms of action for the FDA to feel comfortable in approving it.

comfortable in approving it.

The entire problem that the FDA had with Ergo Science's case can be summed up in one sentence: "I think there are a lot of unanswered questions and so I think we just need more data." (pg. 242) Ignoring all of the details I presented above, that was the bottom line.

Had Ergo Science waited a year or two, done a few more clinical studies with larger and more diverse groups, had mechanistic data on how the drug works in humans, and presented their case more strongly, the FDA would have most likely approved it. Quite in fact, in closing out the proceedings, two statements by FDA committee members stand out. The first was: "I think the science that has been presented is excellent. We just need more defined data in humans and longer term data." (pg. 246)

The second, by a different committee member was:

"At the same time, you know, that's an area that is, I think, very important; namely that I think that the brain has a critical role to play in metabolism, and this is the first drug proposed to approach the problems. Nevertheless, I think that if we saw a little stronger data we could have improved it on this go around. I think we need longer data to show durability before approval." (pg. 246)

And that was the end of that. Once again, had Ergo Science had a bit more extensive data, and a few pieces that they lacked, or had they applied now (with more of the mechanistic data available), the odds are that the FDA would have approved it. Instead, since Ergo Science jumped the gun, and took their drug to the FDA without the necessary data, they weren't able to prove their case, and didn't get the approval that they sought.

Frequently Asked Questions

Q: Why bromocriptine?

A: On top of all of the other questions I've received via email, probably the main one is simply Why bromocriptine? Basically, folks want to know why I focused primarily on bromocriptine which, admittedly, may not be ideal since it only activates D2 receptors. As I talked about above, a drug that activated both D1 and D2 receptors would be more ideal.

There are a few reasons. The first, as I discussed early in this book has to do with a few realities: compared to other drugs that are out there bromocriptine is far better researched and more readily available. We also know the risks to a far greater degree. It's also one of the only DA drugs that has actually been tested directly for fat loss.

Basically, I probably could have just talked generally about the DA system and its role in fat loss and that would have been fine. I picked bromocriptine because it's cheap, well-researched, and we know the potential benefits and risks. You can't say that about many of the other drugs out there.

However, that isn't to say that other drugs might not be as, or even more, effective. As I mentioned above, pergolide is a combination D1 and D2 agonist and would be expected to have more potent effects than bromocriptine. Except that it's expensive and would be nearly impossible to get. There are other drugs, such as selegiline (which is actually a dopamine reuptake inhibitor, meaning that it prevents neurons from re-absorbing DA from the neuronal space) which some have suggested for the effects described in this booklet. Would they work? Yeah, probably. But there's no research and I did enough speculating already.

On that note, I did want to mention a relatively new drug with DA action that has been shown to affect weight loss while dieting. It's called Wellbutrin (aka bupropion) and actually acts as a combination DA and norepinephrine reuptake inhibitor. Wellbutrin is actually used as an anti-depressant and for stopping smoking but two recent studies showed that dosing it at 300-400 mg/day increased weight loss in obese dieters (86a,86b).

Since it also affects noradrenaline levels in the brain, Wellbutrin might actually

be a better drug for fat loss and dieting. Stacking it with a serotonin drug (such as one of the many Serotonin reuptake inhibitors) would be similar to stacking Bromocriptine (or another pure DA drug) with Meridia (a serotonin and noradrenaline reuptake inhibitor). Basically, the combination of drugs would allow all three of the brain's primary neurotransmitters to be controlled during dieting.

Q: Can I stack bromocriptine with drug XXX?

A: This is a question I've gotten several iterations of via email. Unfortunately, as I mentioned in the book, there simply isn't a lot of information on possible interactions with other drugs, beyond what I mentioned.

As stated in the booklet, the use of sympathomimetic drugs (drugs that mimic the catecholamines such as ephedrine and clenbuterol) appears to inhibit the effects of bromocriptine. So they can't be used. As I mentioned in the booklet, they shouldn't really be necessary for the most part. A few other compounds I've gotten questions about.

Phentermine: This is a sympathomimetic drug, it can't be used with bromocriptine. In fact, most appetite suppressants fall into this category of drugs and can't be used (fenfluramine, which works through a different mechanism should be ok). As I've said before, they shouldn't be necessary since bromocriptine will keep hunger under control anyhow.

Caffeine: I don't see any problem using this with bromocriptine.

Yohimbe: I don't see any problem using this with bromocriptine. Although it is affecting adrenoreceptors, it is doing so somewhat passively, by inhibiting the effects of alpha-2 receptors. It isn't acting as a true sympathomimetic drug.

Glucophage (metformin): Glucophage improves insulin sensitivity peripherally, while bromocriptine appears to exert its effect centrally. From the standpoint of improving insulin sensitivity (for either diabetic or performance reasons), I suspect they'd work

well together. I don't see any problem using them together, except for the possibility of hypoglycemia. This would especially be true on lowered carbs.

Q: What about stacking bromocriptine with nicotine?

A: Both nicotine and bromocriptine work through the dopamine system (nicotine raises dopamine levels, bromocriptine mimics dopamine). This is probably part of why nicotine acts as a potent appetite suppressant, on top of stimulating metabolism. Nicotine also has direct effects on fat mobilization at the fat cell.

Personally, except for the peripheral effects, I don't see any real reason to stack nicotine with bromocriptine. Since both work through the dopamine system, I doubt that you'd get any type of synergistic effect. As well, I'd be concerned about increased side-effects from too much dopamine receptor stimulation.

It is possible that using nicotine (i.e. the gum or the patch) would allow lower doses of bromocriptine to be used. I haven't gotten any feedback on this so you'll have to try it and see if you so desire.

Q: What about stacking bromocriptine with DNP?

A: Apparently DNP usage is still occurring in the hardcore bodybuilding world and I've received questions about bromocriptine and DNP a number of times. Before, I answer it I want to make something very clear: I do not in any way, shape, or form endorse or encourage the use of DNP. Yes, I did use it several years ago, although that was more out of personal curiosity/experimentation; I've never had any desire to use it again. The potential risks are simply too high IMO. However, recognizing that some people will still use it, I feel compelled to answer the question.

For those who don't know, DNP is a chemical compound that uncouples energy production in the mitochondria, causing energy to be wasted as heat. While this burns off fat at a tremendous rate, it is also extremely dangerous as a DNP overdose

can kill you outright. Take too much and you overheat and cook from the inside out.

With that said, DNP can be used with bromocriptine. Although a thermogenic, DNP does not work through the typical sympathomimetic pathways (such as ephedrine/caffeine and clenbuterol). Hence, there should be no direct interaction between the true drugs. As well, since DNP causes such rapid fat loss, I would expect it to cause leptin to plummet (inducing the standard set of dieting adaptations). Using bromocriptine simultaneously with DNP (to prevent the normal adaptations) or when ending a DNP cycle (to prevent rebound fat gain) makes physiological sense and should work.

Q: Is bromocriptine lowering my setpoint?

A: No. The setpoint appears to be set in the hypothalamus based on the neural connections and levels of various neurotransmitters. By maintaining a normal dopamine signal in the face of fat loss, bromocriptine is essentially tricking your body into thinking things are normal. But your setpoint isn't changing. A true change in setpoint would mean that your system is now running normally at a lower bodyfat percentage than before. Based on research done to this point, lowering setpoint permanently is impossible.

If you're having trouble understanding this, here's a rough analogy. You can sort of think of your setpoint as being sort of like the thermostat in your house. So say you have your thermostat set to 80 degrees. If temperature drops to 75 degrees, your thermostat notices it and turns on the heat. Basically, the thermostat adapts your heating system when temperature drops below a certain level.

The setpoint is similar: say your hypothalamus is set at 15% bodyfat, that is, 15% bodyfat is your setpoint. It's monitoring various chemicals and if you go below 15% bodyfat, it tells your body to adapt.

Ok, so let's say that the temperature in your house dropped to 70 degrees. But let's say that you put a small heating pad on your thermostat. Even though the external

temperature is below the thermostat's setpoint, the heater is tricking it into thinking the temperature is still normal. Hence, the heat (adaptation) doesn't turn on.

Same thing with bromocriptine. Your hypothalamus still wants to see certain levels of neurotransmitters (related to leptin). Bromocriptine is simply tricking your hypothalamus into thinking everything is normal.

Truly lowering setpoint would mean changing how the hypothalamus is wired (it would be analogous to moving the switch on your thermostat down to 75 degrees). As I said above, based on the research done so far, this doesn't ever appear to occur.

Q: Do I need to cycle bromocriptine?

A: I'm not sure how I forgot to address this originally but it's a good question. As mentioned in chapter 8, safety reviews of bromocriptine indicate that it has been used in various patient populations from 1-10 years. This tells me two things. First is that the long-term effects of bromocriptine are no different than the short-term effects; there doesn't appear to be any increased risk from staying on it year round. As well, the fact that patients are kept on the drug year round suggests no loss of effect with long-term use. That is, the body doesn't appear to adapt or downregulate DA receptors in response to activation via bromocriptine. I see no need to cycle it.

Q: When/if I come off of bromocriptine, will my metabolism still be fixed?

A: This relates to the previous question and, sadly, the answer is no. Most drugs are only temporarily fixing whatever defect is occurring. The changes are rarely permanent.

So if you have low testosterone and you supplement with steroids, when you go off the steroids, you don't magically have normal testosterone levels. If you have low thyroid levels, and use thyroid drugs to fix it, your metabolism won't magically be fixed when you stop the drug. If you have low sympathetic nervous system output and you use

ephedrine/caffeine or clenbuterol to fix it, your system won't magically be fixed when you stop using the drug. All you did was temporarily fix the system while you were on the drug.

Same deal here. Bromocriptine will only keep your metabolism fixed as long as you are on the drug. Related to that, I've gotten questions as to whether folks should expect a rebound fat gain if they go off of the bromocriptine.

That, of course, will depend on the rest of what you're doing. Yes, if you go off of bromocriptine after you've dieted to a low level of bodyfat, you can expect your metabolism to start adapting: slowing metabolism, fat burning, increasing hunger, etc. If that makes you start overeating, of course you'll gain back the bodyfat.

Q: What's the best way to come off of bromocriptine, if I decide to do so?

A: The first thing I would suggest is bringing calories back to approximately maintenance levels. Even increasing calories to this level will help bring leptin levels back up to some degree. Yes, they'll be lower than when you were fatter, but they'll be higher than if you were still dieting. Staying at that level for a week or two will help to renormalize the system to some degree.

Along with that, reducing the dose of bromocriptine should help to avoid hunger screaming off the charts, or metabolism crashing too hard and too quickly. Yes, you can expect both adaptations to occur but it shouldn't be as severe. Assuming you're using 5 mg/day to begin with, reducing to 2.5 mg/day for a week while you're raising calories slightly would seem to be the best strategy.

As well, reintroducing something like the ephedrine/caffeine stack would also be a very good idea as you reduce the dose of bromocriptine. Although EC doesn't fix all of the metabolic problems, it does help to maintain nervous system output and control hunger and appetite. Obviously maintaining (or even slightly increasing) activity will also help to avoid fat regain.

Beyond that, staying at your newly achieved lower bodyfat level, if you go off of

bromocriptine, will come down to simply controlling your food and activity. It's not fun but can be done. Inserting a 12-24 hour period of relatively free-for-all eating each week can also be helpful for both psychological and physiological reasons. Very lean individuals can probably benefit from 2X12 hour periods of overfeeding per week. Not only does this help bump leptin a little bit, fat gain during such a short period is nearly impossible. Just keep carbs high, fat lowish, and protein moderate and try to synchronize it with your intensive weight training days.

Q: What's next on the horizon?

A: I firmly believe that the future body recomposition is in fixing the brain. Frankly, we've reached the limits of what we can do to muscle and fat cells with drugs and nutritional approaches.

The brain is, fundamentally, coordinating the entire system. Yes, the entire system is integrated but the brain is still handling most of it. If your brain is wired badly, there's simply going to be a limit to what you can achieve, especially naturally. Most supplement and drug strategies to date have focused entirely on the rest of the system, without fixing the fundamental problem.

Yes, fine, we can boost testosterone levels with drugs or prohormones and that has an effect. But that still doesn't correct the overall problem, which is that your body's setpoint for testosterone production (set via the HPTA) is dysfunctional. Finding a way to reset the HPTA would have a greater effect, without a rebound problem.

I liken it to buying a car with a shitty engine. Yeah, fine, you can put the best wheels, a spoiler, an airdam, all of that on your car but it will still suck. Because the engine sucks. A better engine gives better results overall.

In this case, focusing only on fat cells or muscle cells or the pancreas is like fixing the wheels and the rest of your car. It helps but it leaves the fundamental problem, your brain, the engine that's driving the entire system unfixed. Altering/modifying brain chemistry to change the basics of the whole system is the future of body recomposition.

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