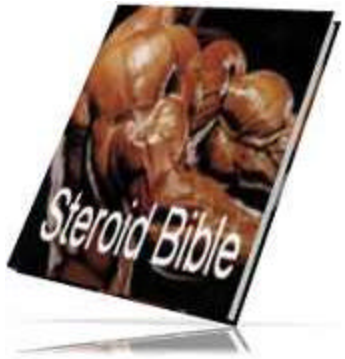
Introduction to Anabolic Steroids



How do anabolic steroids differ, and why do they have differing effects? How do they work? When and how much of what steroid should be used, and why?

It is one thing for writers to make statements about anabolic steroids, and to make recommendations. Some of what they say may be good, but some may be bad. It's my goal to give you the understanding, when you read about steroids, to judge for yourself what is being said. When you understand how they work, then you can understand for yourself whether a given claim or idea is a good one or not.

In the next few articles, I will give you the background to have a good understanding of how these drugs work, so that you can develop informed plans for their use.

Mechanism of Action

First, let's take the broadest view possible, but at the molecular level. Consider one molecule of an anabolic/androgenic steroid (AAS) in the bloodstream, bound to a molecule of testosterone binding globulin (TeBG). A receptor on the outside of the muscle cell will bring the TeBG/AAS into the cell. This process itself stimulates the metabolism of the cell by increasing cyclic AMP, but that is not the major effect of AAS use.

Alternatively, the AAS molecule may be free in the bloodstream, not bound to anything. If so, it can easily diffuse into the cell through the cell membrane, rather like water soaking through paper.

Next, inside the cell, the molecule of AAS binds to a molecule of androgen receptor (AR), which is inside the cell, not in the cell membrane. The androgen receptor is a very large molecule and is made of about a thousand amino acids. Thus, it is far larger than the

molecule of AAS. The AR has a "hinge" region, and can be folded into either of two shapes. When it binds a molecule of AAS, the AR folds at the hinge, and is activated.

Think of the AR as being a machine that does nothing unless it is turned on. The AR either has an AAS bound to it, and is thereby switched on; or it does not, and is switched off. There is no intermediate condition that might cause an AAS to give a weak effect – there is no being "halfway folded" at the hinge. The only question is, How long does the AR stay activated before the AAS leaves? The answer, generally, is in the range of a couple of hours.

After the AAS leaves, the AR returns to its original state, and is ready to be used again.

Since the AR can only be either activated or not activated, it is just as much activated by say a bound molecule of methenolone (from Primobolan) as it is by a bound molecule from any other AAS.

This is not to say that differing AAS may give differing results for other reasons.

Once a molecule of AAS is bound to the AR, the receptor now travels to the nucleus of the cell, and forms a dimer (pair) with another activated AR. The dimer then binds to certain parts of the DNA, and certain genes then start producing more mRNA. This is a way for the body to selectively activate only certain genes. In this case, only those genes associated with androgens are activated, or have their activity increased.

mRNA is different for each gene, and carries the information the cell needs to make specific proteins. Myosin and actin, which are major components of muscle, are examples of proteins, and these are made, ultimately, as a result of mRNA production from the genes for those proteins.

At last: muscle protein, our goal. The molecule of AAS ultimately causes the muscle cell to make more of certain proteins, helping the user to get bigger. (There were steps needed to get from the mRNA to the protein, but we will skip them.)

Does each binding of AAS to an AR result in exactly one extra molecule of protein produced? No. Because even though the AR is fully activated by any AAS, that does not mean that it always succeeds in binding to DNA. And differing amounts of mRNA might be produced, because an AR remains active as long as an AAS remains bound to it. If many mRNA molecules are produced, then, generally, they will cause many corresponding protein molecules to be produced.

So the amount of extra growth per extra activated AR can vary.

The Androgen Receptor

Now, having a broad view of the process, let's take a closer look at the AR itself.

The AR is a large protein molecule, produced from one and only one gene in DNA. There aren't lots of different kinds of receptors, as some authors claim. There are not, for example, ARs specific for oral or injectable anabolics, nor for different esters of testosterone, nor for any different kinds of AAS.

The first important question to ask is, "How many ARs do you have? Is the number small or large? Can it be changed?" Since these are, in effect, little machines which are either on or off, and their effect is greater as more are activated, we want as many of them switched on as possible.

There are far fewer ARs than most people realize. Some authors who are opposed to AAS doses beyond 200 mg/week say that only this amount will be accepted by the receptors in muscle, and everything past that will "spill over" and go into receptors in the skin and elsewhere.

Research shows that muscle tissue has, roughly, 3 nanomoles of ARs per kg. Then your body probably has less than 300 nanomoles of ARs, grand total, let's say.

Well, one 2.5 mg tab of oxandrolone supplies about 8000 nanomoles of AAS. Clearly, that's far more molecules than your body has receptors.

A little math shows that all those receptors combined could bind only a small percentage of the molecules of AAS in one little 2.5 mg tab. So binding to ARs cannot appreciably reduce the concentration of AAS in the blood. Therefore, the ideas that ARs will bind most of whatever dose some author recommends, or that "spill-over" will occur beyond that, are entirely wrong. There just aren't that many receptors.

Typical doses of AAS are high enough that a high percentage of the ARs are bound to AAS, whether the dose is say 400 mg/week or 1000 mg/week. If similar percentages of ARs are active – close to 100% in each case -- then why do higher doses give more results? It's a fact that they do, but there is not any large percentage of unoccupied receptors at the moderate dose. Thus, there is little room for improvement there. So at least part of the cause must be something other than simply occupying a higher percentage of receptors.

And why did I pick those doses, rather than comparing normal levels with say 400 mg/week?

The fact that the ARs must form dimers to be active has an interesting consequence. The mathematics are such that if two ARs must join together to form an activated dimer, and both must bind a molecule of AAS, then the square must be taken of the percentage. This means that if say 71% of receptors are binding steroid, only 50% of the dimers will be activated. Thus, at low levels, there is more room for improvement than one would think.

But if say 95% are occupied, then even after squaring that, there would still only be 10% room for improvement.

But actual improvement – increase in effect – seems to be much more than 10%. Anabolism increases even as the dose becomes more than sufficient to ensure virtually complete binding. Why?

One popular explanation is that high doses of AAS block cortisol receptors and are thus anti-catabolic. But if this were an adequate explanation, then one could use anti-cortisol drugs together with low doses of AAS and get the same results as with high doses of AAS. This isn't the case. In fact, if cortisol is suppressed, this simply results in painful joint problems. And if the cortisol-blocking theory were true, we also would expect that persons with abnormally low cortisol ought to be quite muscular. That isn't the case either.

Three other possibilities come to mind:

Possible Explanations for the Effect of High Dose Anabolic- Androgenic Steroids

High doses of AAS could upregulate AR production

Although activity cannot be greatly increased by increasing occupancy of existing receptors, it might potentially be greatly increased by increasing the number of receptors. This is mentioned here as a possible explanation for the effects of high dose AAS, not as an established observed fact in muscle tissue of bodybuilders. I am not aware of any such studies.

Upregulation is observed from supraphysiological doses of nonaromatizing AAS in other tissues, and is observed in humans in response to resistance exercise.

High doses of AAS could stimulate growth independently of the AR

In muscle tissue, androgen has been observed to activate the immediate-early gene zif268 in a process not involving the AR. This activity is almost certainly related to muscle growth, and it requires high doses.

Testosterone is observed to increase the efficiency of mRNA translation of cellular proteins, and this may be mediated by a mechanism independent of the AR.

Nerve tissue has been observed to respond almost instantly to androgen. This cannot be a result of the AR mediated process I have described here, because that process takes much more time.

Generally speaking, the hypothesis that a drug acts by only one mode of action can be tested by examining the dose/response curve. If an effect is dependent only upon the activity of a receptor, then the log response should follow a sigmoidal function (an S shaped curve). The graph would be nearly flat both at low and high doses, and approximately linear at moderate doses.

At moderate doses the linear function is indeed seen.

The problem is, for the range of approximately 100 to 1000 mg/week, the graph remains linear regardless of dose! By the way, this does not mean that twice the dose gives twice the effect. Rather, about four times the dose is required to give twice the effect.

This response is not consistent with a simple receptor-only model; such a model is not supported by the dose/response curve. But this type of response is to be expected if there are other variables besides receptor binding. This can be explained if one or more of the mechanisms is saturated at lower levels of drug, and one or more other mechanisms do not become saturated until much higher levels of drug are used.

High doses of AAS might improve the efficiency of action of ARs

Not only the number of ARs is important, but also their efficiency of operation. The entire process, as was partially described above, involves many proteins, some of which may be limiting. Increases in the amounts of these proteins might increase activity dramatically. For example, ARA70 is a protein which can improve the activity of the AR by ten times.

I am not aware of any study determining how ARA70 may be regulated by high doses of AAS. I cite this as an example of the type of pharmacology that may be going on, and also, incidentally, as a potential target. If you happen to see where some other drug has been seen to increase ARA70, that might be very interesting!

Other proteins which can affect efficiency include RAF, which enhances the binding of the AR to DNA by about 25-fold; GRIP1, and cJun. None of these, unfortunately, could themselves be taken as drugs.

But you can see that there are many ways by which AR activity could change besides any "upregulation" or "downregulation" of receptors. Authors who make such claims as the be-all and end-all of their steroid theories essentially do not know what they are talking about. Without specific evidence – without actual measurement of AR levels – it is always unjustified to claim that "androgen receptor downregulation must have occurred," especially on the basis of anecdotal evidence. Actual measurements are always lacking from such claims.

Nor is it justified to assume that increasing the occupancy of ARs is the only way to increase the effect of androgens, as we have seen. It is justified, on the basis of real world results, to say that high dose AAS are more effective than low dose AAS, and certainly

more effective than natural levels of AAS. This is true even if use is sustained over time. That however is not consistent with any claims of downregulation of androgen receptors in response to high doses of AAS.

It also is justified both from bodybuilding experience and from scientific evidence that low AAS doses, such as 100 or 200 mg/week, will generally not give much results for male athletes.

Next, we will consider regulation of the androgen receptor more closely. There have been many opposing claims concerning this. Which claims are valid? How should these theories affect an athlete's planning?

Androgen Receptor Regulation

One of the most common beliefs concerning anabolic/androgenic steroid (AAS) usage is that the androgen receptor (AR) downregulates as a result of such usage. This has been claimed repeatedly in many books and articles, and it is claimed constantly on bulletin boards and the like. If I've heard it once, I've heard it a thousand times. If it were just being stated as an abstruse hypothesis, with no practical implications, with no decisions being based on it, that might be of little importance.

Unfortunately, this claim is used to support all kinds of arguments and bad advice concerning practical steroid usage. Thus, the error is no small one.

We will look at this matter fairly closely in this article. However, in brief the conclusions may be summed up as follows:

• There is no scientific evidence whatsoever that AR downregulation occurs in human muscle, or in any tissue, in response to above normal (supraphysiological) levels of AAS.

• Where AR downregulation in response to AAS has been seen in cell culture, these results do not apply because the downregulation is either not relative to normal androgen levels but to zero androgen, or estrogen may have been the causative factor, or assay methods inaccurate for this purpose were used, or often a combination of these problems make the results inapplicable to the issue of supraphysiological use of androgens by athletes.

• AR upregulation in response to supraphysiological levels of androgen in cell culture has repeatedly been observed in experiments using accurate assay methods and devoid of the above problems.

• AR downregulation in response to AAS does not agree with real world results obtained by bodybuilders, whereas upregulation does agree with real world results. (A neutral position, where levels in human muscle might be thought not to change in response to high levels of androgen, is not disproven however.)

• The "theoretical" arguments advanced by proponents of AR downregulation are invariably without merit.

The belief that androgen receptors downregulate in response to androgen is one of the most unfounded and absurd concepts in bodybuilding.

While this may seem perhaps an overly strong condemnation of that view, please consider that the claims for downregulation seen in books such as Anabolic Reference Guide (6th Issue), World Anabolic Review, Underground Steroid Handbook, etc. are presented with absolutely no evidence whatsoever to support them. The authors merely *assert* downregulation. They have done it so many times that by now many people assume it is gospel. In this paper you will be provided with evidence, and the evidence does not support their claim.

Overview of Regulation

Meaning of regulation

"Regulation" of a receptor refers to control over the number of receptors per cell. "Sensitivity," in contrast, refers to the degree of activity each receptor has. It is a possible in many cases for the receptors of a cell to be sensitized or desensitized to a drug or hormone, independently of the number of receptors. Similarly, it is possible for the receptors to upregulate or downregulate, to increase or decrease in number, independently of any changes in sensitivity.

If sensitivity remains the same, then upregulation will yield higher response to the same amount of drug or hormone, and downregulation will result in less response.

So if we are discussing androgen receptor regulation, we are discussing how many ARs are present per cell, and how this may change.

Changes in regulation must, of necessity, be between two different states, for example, levels of hormone. In the case of bodybuilding, we are interested in supraphysiological levels vs. normal levels (or perhaps, a higher supraphysiological level vs. a lower supraphysiological level.) In most research that is done, the comparison is often between normal levels and zero levels, or the castrated state.

We may describe regulation with the two levels being in either order. Upregulation as levels decrease from normal to zero is the same thing, but in the reverse direction, as downregulation as levels increase from zero to normal.

The term which would be used will depend on context, but does not change meaning, so long as the direction of change in level of hormone is understood.

If upregulation occurs as levels decrease from normal to zero, as is probably the case in some tissues, this would imply nothing about what may happen as levels increase beyond normal. It does not prove that downregulation would occur. It would be a serious error to take a study comparing normal levels and zero levels and use that study to argue the effect of supraphysiological levels. Unfortunately, such mistakes are commonly made by authors in bodybuilding.

Forms of regulation

Broadly speaking, there are three things that control the number of receptors. To understand them, let's quickly review the life-cycle of an individual AR.

There is a single gene in the DNA of each cell that codes for the AR. In the *transcription* process, the DNA code is copied to mRNA. The rate (frequency) of this process can be either increased (promoted) or decreased (repressed) depending on what other proteins are bound to the DNA at the time. Increase or decrease of this rate can be a form of regulation: the more AR mRNA is produced, all else being equal, the more ARs there will be. However, all else rarely is equal.

If efficiency is 100%, each mRNA will be used by a ribosome to produce an AR, which is a protein molecule. The process of making protein from the mRNA code is called *translation.* In practice efficiency will not be 100%. Changes in efficiency of translation can also be a form of regulation.

The third contributing factor to regulation is the rate of loss of ARs. If the cell produces *x* ARs per hour, and their half life is say 7.5 hours, then the number of ARs will be higher than if ARs are produced at that same rate but the half life is say only 3.3 hours. Thus, control of rate of *turnover,* or change in half-life, can be another means of regulation.

The Arguments for Downregulation

Arguments from the popular literature

I am indebted to one of my former colleagues at *Dirty Dieting* for contributing these first several arguments, which are from one of his published articles. I could never have thought of them myself:

"Users of anabolics certainly have elevated levels of androgens, but they have very few testosterone receptors in their muscles…The paradox for natural bodybuilders is that they have plenty of receptors but not enough testosterone."

Response: there are no studies in the literature demonstrating any such thing. The above statement is an assertion only, and therefore cannot be accepted as evidence that AAS use in athletes downregulates the AR.

"Users of anabolics, on the other hand, have more androgens than they need, so their training should be oriented exclusively toward re- opening the testosterone receptors."

This statement deals with the issue of sensitivity, not of regulation, but again the claim is unsupported. Users of anabolics find value in the increased doses of androgen, and advanced users may well need all that they are using simply to maintain their far-above-normal mass, let alone gain further mass. The reference to "re-opening" the testosterone receptors is dubious at best, since the receptors are not closed, nor is their any indication in any scientific literature that such could possibly be the case, or that some given style of training will remedy any such (nonexistent) condition.

"One group [natural trainers] needs more testosterone, the other needs more receptors. Each group needs what the other has-which is the very reason that the first cycle of anabolics has the most effect."

The statement that the first cycle has the most effect is true, in my opinion, only by coincidence. More accurately, the cycle starting at the lowest muscular bodyweight will have the most effect. This may be because the closer you are to your untrained starting point, the easier it is to gain.

Let us look at the example of a person who achieved excellent development with several years of natural training and then has gained yet more size with several steroid cycles. He then quits training for a year and shrinks back almost to his original untrained state.

If he resumes training and uses steroids, will his gains be less than in his first cycle? Hardly. So what that it may be his fifth or tenth cycle, not the first? There is no counter inside muscle cells counting off how many cycles one has done. In examples that I know of, the gains in such a cycle have been *greater* than in the first cycle. (No, that does not prove upregulation, but it is strong evidence against the permanent-downregulation-after-first cycle "theory.")

The greater the gains one has already made, the harder further gains are. This is true under any conditions, regardless of whether AAS are involved or not.

Thus the "first cycle" argument proves nothing with regards to AR regulation.

In any case, regulation is a short term phenomenon, operating on the time scale of hours and days. But if it were permanent or long-lasting as this writer believes, then if steroid use were ceased for a long time, one ought to shrink back to a *smaller* state than was previously achieved naturally, despite continuing training. After all, one would have fewer receptors working, having damaged them forever (supposedly) with the first cycle.

That is, of course, not the case. Which is not surprising, because the "theory" is medically ridiculous.

"Various bodybuilding publications have recently featured articles stating that as a bodybuilder's level of androgens increases, so does the level of testosterone receptors in his muscles. In other words, testosterone is said to be able to upregulate its receptors in the muscles. Needless to say, the more testosterone receptors you have, the more anabolic testosterone will be. The result of the above reasoning is that it gives license to a11 sorts of excesses."

Whether it "gives license to all sorts of excesses" or not has nothing to do with whether it is true.

"First of all, if the theory were true, sedentary persons using androgens -- for contraception, for example -- would become huge. The extra testosterone would increase the number of testosterone receptors. The anabolic effect of testosterone would become increasingly stronger. In reality, untrained people who use steroids have very limited muscle growth. hey rapidly become immune to testosterone's anabolic effect. That doesn't sound like androgen receptor upregulation, does it?"

First, no one has claimed that weight training is not needed for the steroid-using bodybuilder. This is a strawman argument. Resistance training is demonstrated to upregulate the androgen receptor, for example, and also stimulates growth by other means. Therefore it is not surprising that those who do not train do not gain nearly as much muscle as those who do. The argument that AAS use alone, without training, will not produce a championship physique proves nothing with respect to how the androgen receptor is regulated. It does not even suggest anything, to any person with judgment.

And the concept that upregulation could only exist as an uncontrollable upwards spiral is entirely incorrect. Rather, for any given hormone level, there will be a given AR level. There is no feedback mechanism, not even a postulated one, where this would then lead to yet higher hormone level, leading to yet higher AR level, etc. In fact there is negative feedback, since upregulation of the AR in the hypothalamus and pituitary in response to higher androgen would lead to greater inhibition of LH/FSH production, and therefore some reduction in androgen production.

In the case of sedentary subjects, let us use the subjects in the NEJM study, who received 600 mg/week testosterone, as our example. While I do not know if these subjects did experience AR upregulation in their skeletal muscle tissue, if their receptor numbers had let us say increased by some percentage, there would come some point in increased muscle mass where catabolism again matched anabolism, and further growth would not occur. No runaway spiral of muscle growth would be expected either. Thus, my colleague is arguing against non-issues.

Lastly, such persons do not, as he claimed, become immune to testosterone's anabolic effect: they maintain the higher muscle mass so long as they are on the drug.

"*After all, the heaviest steroid users are found among bodybuilders. In those heaviest users there should be upregulation of androgen receptors. If that were true, here's what*

would happen. The androgens would cause their receptors to multiply and get increasingly more potent as time went on. If androgen receptors were truly upregulated that way, steroid users would get their best gains at the end of a cycle, not the beginning, and professional bodybuilders would get far more out of their cycles than first-timers."

There is no reason to think that upregulation would become "increasingly more potent as time went on." Control of regulation is fairly quick.

The concept that AR activity is measured by "gains" is simply ridiculous. The function of the activated AR is not to produce gains per se, but to increase protein synthesis. That will only result in gains if muscle catabolism is less than the anabolism. As muscle mass becomes greater, so does catabolism. At some point under any hormonal and training stimulus, equilibrium is reached, and there are no further gains. With high dose AAS use, that point is at a far higher muscle mass than if androgen levels are at only normal values. The concept that the steroids are "not working" for the

bodybuilder who is maintaining 40 lb more muscular weight than he ever could achieve naturally, and who might even still be gaining slowly (but not as fast as in his first cycle) is, at best,an example of poor reasoning..

Moderate dose steroids, even though they are sufficient to saturate the AR, don't take one as far as high dose steroids can. The difference cannot be substantially increased percentage of occupied receptors, since almost all are occupied in either case.

What does that leave as the possibilities? More receptors, or non-receptor-mediated activity.

Is there evidence that muscles are more responsive to the same level of androgen after having been exposed to high dose androgen? That would be the case, at least temporarily, if upregulation occurred. The answer is yes, there is such evidence, anecdotally. If a brief cycle (2 weeks) of high dose AAS with short-acting acetate ester is used, there can be substantially increased androgenic activity, relative to baseline, in weeks 3 and 4 even though the exogenously-supplied androgen is long out of the system. This is what would be expected if upregulation occurred. It could not be the case if substantial downregulation occurred.

"The longer a course of treatment lasts, the more users are obliged to take drugs to compensate for the loss of potency."

This is simply untrue. I know of no cases of steroid users who found that they began losing muscle mass while remaining on the same dose. The illogic here is confusing cessation or slowing of gains with cessation of effect. One instead should look at,. What muscular weight set-point is the body experiencing with this hormonal and exercise stimulus?

With higher dose AAS, that setpoint is higher. Once it is nearly achieved or achiever, of course gains slow or stop. And besides this, even if the body has not yet fully achieved the higher mass that may be possible with a given level of AAS, it is harder for many reasons for the body to grow after it has recently grown a fair deal. It needs time before being ready to again grow some more. This is observed whether steroids are involved or not.

The illogic of people who correlate rate of gains with AR level is amazing. I suppose they would have it that the AR downregulates after the first 6 months of natural training as well. After all, gains slow down then.

"Androgen upregulation would take place in every single muscle, not just in the exercised muscles. Consequently, a user of anabolics who only trained his arms should see his calves grow. That's not the case, however, even for the professionals. I wish it were true, as they wouldn't look so silly with their huge arms and puny calves. I don't have to keep demonstrating that the theory is just plain stupid. It is refuted daily by the experiences of bodybuilders who use anabolics, as well as by the research."

Again, no one claims that training is not also required for muscles. No one ever said that AAS use alone is sufficient to induce muscular growth far past the untrained state. This same logic used above could be used to argue that steroids do nothing whatsoever. After all, if they worked, then you would not need to train your calves, you could just train your arms.

The assertion that upregulation is refuted daily by the experiences of bodybuilders, or by research, is just that: an assertion.

"The fact is, excessive androgen levels induce the rapid loss of muscle testosterone receptors."

The fact is, the author had to cite some utterly obscure journals in the Polish language to support his claim. I rather doubt that were I able to read Polish that I would find the actual article to support his claims.

"There is absolutely no increase. The muscle fights the excess and immunizes itself against androgens, which is the reason steroids become less potent as time goes by."

The statement that the body immunizes itself against androgens is medically incorrect. The statement is severely enough in error that one must doubt the competence of the author to discuss any medical or physiological matters, and casts grave doubt on his judgment in such manners. Thus his statements cannot be accepted by his authority: he has none. Nor are they supported by any facts.

Let us then move on to more serious arguments to be found in the scientific literature:

Scientific Evidence Apparently Favoring Downregulation

While there are no studies showing downregulation in human skeletal muscle resulting from high-dose AAS use, there are some studies in cell culture, and sometimes *in vivo*, which seem to indicate that downregulation can occur, though not as a result of increase in androgen from normal to supraphysiological.

This is seen both by measurement of AR mRNA, which is in an indicator of the rate of AR production, and in measurement of receptor number.

All of these studies, however, are flawed from the perspective of the bodybuilder wishing to know if downregulation of the AR has ever been observed in any cell in response to increase of androgen from normal to supranormal levels.

Range of measurement

First, the question is, downregulation relative to what? What is the control?

Unfortunately, the control for *in vivo* studies is castration, not the normal state. The bodybuilder really doesn't care if normal testosterone levels may result in fewer ARs for some cell types than would be seen with castration. We would not want to get castrated just to have more ARs than in the intact condition, if for no other reason than that the decrease in androgen level would be more significant than any possible increase in AR number.

In vitro studies have generally been done with zero androgen as the control, not normal androgen.

It cannot be projected that if AR number decreased as testosterone level was increased from zero to normal, that therefore it would continue to decrease as level was increased yet further. For example, the cause of this might be that there is a promotion mechanism increasing AR mRNA production as testosterone levels fall to zero. That would not mean that there would be any loss as testosterone levels increase past normal. Or if it is a repression mechanism that comes into play as testosterone levels rise past zero, that mechanism might be fully saturated by the time levels reach normal, and no further repression might occur as levels go past normal.

In fact, papers which report downregulation, even in their titles, often show in the actual data that the range of downregulation was entirely between zero and normal, or even zero and a subnormal level. Thus they give no evidence whatsoever of downregulation occurring with supraphysiological levels of androgen relative to normal levels.

Estrogen

Testosterone can aromatize to estrogen, which can itself lead to downregulation of the AR. Thus, if a study used testosterone but did not verify that the same results were seen

with nonaromatizing androgen, or did not verify that use of an aromatase inhibitor did not change results, there is no way to know if any observed downregulation is due to androgen or not. It might be due to estrogen.

Assay

Unfortunately, AR concentrations are very low in cells, and mRNA is not so easily measured. It is possible for measurements to be misleading.

In Biochemical and Biophysical Research Communications (1991) 177 488, Takeda, Nakamoto, Chang *et al.* determined, "Our immunostaining [for amount of ARs] and *in situ* hybridization data [for amount of AR mRNA] indicated that in rat and mouse prostate, androgen-withdrawal decreased both androgen receptor content and androgen receptor mRNA level, and that injection of androgen restored normal levels, a process termed 'upregulation'….However, Northern blot data of Quarmby *et al.* in rat prostate have shown a different result, downregulation: the amount of androgen receptor mRNA increased by androgen withdrawal and decreased below the control level after androgen stimulation. *Our preliminary Northern blot data (unpublished data) also showed the same tendency, downregulation."* [emphasis added]

The authors go on to explain in detail, somewhat beyond the scope of this article, why Northern blot analysis can lead to false results. The *in situ* hybridization method is indisputably a superior, more accurate method.

Many of the studies claiming downregulation depend on Northern blot data as the sole "proof." This study, however, shows that such measurement might be entirely wrong. In any case, regulation properly refers to control of the number of receptors. Production of mRNA is one of the contributing factors, but ultimately what must be measured to determine the matter is the number of receptors. This has been done in some experiments.

Specific papers often cited to support downregulation of the AR

Endocrinology (1981) 104 4 1431. This paper compares the normal state of the rat to the castrated state, and the muscle cytosol AR concentrations of the female rat to the intact (sham-operated) male rat.

Objections to this study include the fact that the effect of supraphysiological levels of androgen was not studied; that cytosolic measurements of AR are unreliable since varying percentages of ARs may concentrate in the nuclear region, and these are more indicative of activity; and that castration of rats is notorious for producing false conclusions. The cells, and indeed the entire system of the animal, undergo qualitative change (e.g., cessation of growth) from the castration relative to the sham-operated animals. Testosterone levels are not the only thing which change upon castration. Another objection is that estrogen was not controlled and the effects of estrogen were not determined or accounted for. Estrogen levels certainly were not constant in this experiment.

Molecular Endocrinology (1990) 4 22. AR mRNA level, *in vitro,* was seen to increase as androgen levels were reduced below normal. Supraphysiological levels were not tested. Northern blot analysis was used. AR levels were not measured.

Molecular and Cellular Endocrinology (1991) 76 79. In human prostate carcinoma cells, *in vitro,* androgen resulted in downregulation of AR mRNA relative to zero androgen levels. Levels of androgen receptor, however, increased, relative to when androgen level was zero, by a factor of two. The researchers noted, "At 49 hours, androgen receptor protein increased 30% as assayed by immunoblots and 79% as assayed by ligand binding" [the later method is the more reliable and indicative of biological effect.]

Molecular Endocrinology (1993) 7 924. *In vitro,* it was determined by Northern blot analysis that mRNA levels decreased when supraphysiological levels of androgen were compared to zero androgen in cancer cells. Levels of ARs were measured, and there was no observed decrease despite the observed decrease in mRNA level (as measured by Northern blot.)

Molecular and Cellular Endocrinology (1995) 115 177. COS 1 cells were transfected with human AR DNA with the CMV promoter. The authors state that the DNA sequence responsible for downregulation of the AR is encoded within the AR DNA, not the promoter region. Dexamethasone [a glucocorticoid drug similar to cortisol] was observed to result in downregulation of AR mRNA relative to zero dexamethasone level. Androgen also had this effect, but did not result in lower levels of androgen receptors. This was attributed to increase in androgen receptor half life caused by androgen administration. The observed androgen downregulation effect relative to zero androgen ended at a concentration of 0.1 nanomolar of androgen (methyltrienolone) – higher doses, to 100 nanomolar, resulted in no further downregulation of AR mRNA production.

While this list is not complete, I am not omitting any studies that appear to have any better evidence – indeed, any evidence at all – that supraphysiological levels of androgen result in downregulation, relative to normal androgen levels, of the AR The above is a reasonably complete picture of the research evidence that might be used to support the bodybuilding theory of AR downregulation. When analyzed closely, no scientific study provides support for that theory.

Scientific evidence indicating that a biochemical mechanism for upregulation does exist

Even in the above evidence which *apparently* (at first sight) might seem in favor of downregulation, it was sometimes seen that actual levels of the AR increased, even going from zero to normal (rather than normal to supraphysiological.) This is upregulation of the receptor, since as we recall, regulation is the control of the number of receptors, and this control may be achieved by change in the half life of the receptors. Increased half life of the receptor, all else being equal, or perhaps with change in half-life overcoming other factors, can yield higher receptor numbers. Kemppainen *et al.* (J Biol Chem 267 968)

demonstrated that androgen increases the half life of the AR, which is an upregulating effect.

Endocrinology (1990) 126 1165. In fibroblasts cultured from human genital skin which contained very low amounts of 5-alpha reductase, 2 nanomolar tritium-labeled testosterone [which is sufficient to saturate ARs] produced a 34% increase in androgen receptors as measured by specific AR binding, the best assay method known, and 20 nanomolar tritium-labeled testosterone produced an increase of 64% in number of ARs.

Note: 20 nanomolar free testosterone is approximately 400 times physiological level (normal level in humans is approximately 0.05 nanomolar).

J Steroid Biochemistry and Molecular Biology (1990) 37 553. In cultured adipocytes, methyltrienolone and testosterone demonstrated marked upregulation of AR content upon administration of androgen. 10 nanomolar methyltrienolone increased AR content (as measured by binding to radiolabeled androgen) by more than five times, relative to zero androgen.

J Steroid Biochemistry and Molecular Biology (1993) 45 333. In cultured smooth muscle cells from the penis of the rat, mRNA production was found to be upregulated by high dose testosterone (100 nanomolar) or DHT. When 5-alpha reducatase was inhibited by finasteride, thus blocking metabolism to DHT, AR mRNA production was downregulated in response to testosterone. Blockage of the aromatization pathway to estrogen by fadrozole eliminated this downregulation effect. Estradiol itself was found to downregulate AR mRNA production in these cells.

Endocrinol Japan (1992) 39 235. One nanomolar DHT was demonstrated to increase AR protein by over 100% within 24 hours, relative to zero androgen level. The half life of the AR was demonstrated to increase from 3.3 h to 7.5 h as a result of the androgen administration.

Endocrinology (1996) 137 1385. 100 nanomolar testosterone was found to increase AR levels *in vitro* in muscle satellite cells, myotubes, and muscle-derived fibroblasts.

Conclusions from Scientific Research

As androgen levels decrease from normal to zero, production of AR mRNA may increase in some tissues. However, the number of ARs does not necessarily increase, because the half life of the ARs decreases with lower concentrations of androgen.

As androgen levels increase from normal to supraphysiological, numbers of ARs in some tissues have been shown to increase. Such an increase is upregulation. The increase may be due primarily or entirely to increase in half-life of the AR resulting from higher androgen level.

There is no scientific evidence to support the popular view that AAS use might be expected to result in downregulation of the AR relative to receptor levels associated with normal androgen levels.

Conclusions from Bodybuilding Observations

I find it rather unreasonable to think that the most likely thing is that athletes who have been on high dose AAS for years, and are far more massive than what they could be naturally, and who are maintaining that mass or even slowly gaining more, could possibly have *less* androgen receptor activity than natural athletes or low-dose steroid users.

It might, hypothetically, be possible that their AR activity is the same, and the extra size due to steroids is due entirely to non-AR mediated activities of the androgens. However there is no evidence for that and it seems unlikely.

I believe the most logical possibility is that these athletes are experiencing *higher* activity from their androgen receptors than natural athletes, or low dose steroid users, are experiencing. Since the majority of androgen receptors are occupied at quite moderate levels of AAS, the explanation cannot be simply that a higher percentage of receptors is occupied, with the receptor number being the same. That would not allow much improvement. In contrast, upregulation would allow substantial improvement, such as is apparently the case (unless non-AR mediated activities are largely or entirely responsible for improved anabolism, which would be an entirely unsupported hypothesis.)

Upregulation in human muscle tissue, *in vivo*, is not directly proven but seems to fit the evidence and to provide a plausible explanation for observed results.

I leave the matter, however, to the reader. Weigh the evidence, and decide if downregulation, as popularly advocated, is supported by science, or by what is experienced in bodybuilders.

Anabolic-Androgenic Steroid Cycle Planning

Introduction

In previous issues, we have discussed the pharmacology of anabolic steroids somewhat. However, ultimately, most are interested in having and understanding the answers to very simple questions, such as, "Which steroids should I use? How much of them should be used, and for how long? What other drugs are needed in combination with the steroids?" However there is no single correct answer for everyone.

I do need to stress that there is no recommendation that anyone "should" use these drugs. We are discussing use by those who have already made that decision for themselves.

The first thing to be considered is, "What are the goals?" And perhaps the second thing to be considered is, "Are those goals reasonable or should they be changed?" All too often I am asked questions from people who wish to add a lot of muscle and cut a lot of fat simultaneously and who want to use the mildest and safest drugs and they want to know what they should do. What they should do is to come up with some goals that do not contradict each other. In this article, we will consider goals and how to achieve them. In all cases we refer to use by male users. Females must use much lower doses to avoid virilization problems, and in fact even low dose use may lead to irreversible lowering of voice, increase of facial hair, etc. Therefore, use by women is a separate issue which is not being addressed here.

Muscle Mass

Let us consider the first goal mentioned: gaining muscle mass. Now this goal depends highly on how advanced one already is as a trainer and/or steroid user. Someone who is already 40 lb. more muscular than he could achieve naturally, and who wishes to add still more for the purposes of competitive bodybuilding, will simply find no use from a recommendation to use 500 mg/week of Sustanon. At best such a dose might allow him to maintain what he has, instead of slowly losing muscle while off drugs. Such an athlete will probably not achieve his goals with less than a gram per week of injectables, stacked with at least 50 mg/day of orals. And he may need more than this. He is already far beyond what he could attain naturally, and more yet will not come easily.

What of the person who, after several years of hard, quality training, is probably fairly close to his genetic limit under natural conditions? He would probably achieve excellent results with this same 500 mg/week dose of Sustanon, and undoubtedly would do so with some Dianabol added as well.

Another person may not even be close to his natural genetic limit in the first place, due to inconsistent or poor training, or novice status. Such a person can make excellent gains without anabolic/androgenic steroids (AAS) at all, and while AAS can increase the rate of gains, one cannot say that any particular drug regimen is necessary or advisable.

Yet another person, who simply wishes to have an attractive physique and appearance by conventional standards, and highly values the condition of his skin and hair, would be poorly served by the advice to use Sustanon or Dianabol at any dose. The likely worsening of his skin and possible acceleration of hair loss would not be worth it. He would be better served with a milder drug, which would allow him to achieve his goals with minimal cosmetic or health risk.

Fat Loss

And what about the second goal: losing fat? Well, this goal is at cross-purposes with gaining muscle. One simply cannot gain nearly as much muscle on reduced calories as on higher calories allowing a fat gain of perhaps 1 lb/week. The person would be best advised to divide muscle gains and fat loss into separate phases. If a person is not at a level of muscularity beyond what he can attain naturally, AAS really are not necessary for dieting down to moderate bodyfat levels such as 8%. However, AAS use can make the dieting easier and faster, especially for natural endomorphs. It does not seem that much of a dose is required in this application. 250 mg/week Sustanon or 400 mg/week Primobolan will be effective. That however is not the case for individuals who are well beyond their natural limits. They will shrink much faster on low dose steroids than on high dose steroids while dieting, and anything less than a gram per week would be obviously much less effective than doses actually used (2-4 grams per week not being unusual in elite circles.)

Safety

Estrogenic effects are one of the serious problems with AAS use. Most AAS either convert to estrogen or even if they may not, act to increase the effect of estrogen. Testosterone, Dianabol, and Anadrol are particularly noted bad performers in this regard, and nandrolone (Deca) is not by any means immune to conversion to estrogen. Methenolone (Primobolan), trenbolone, oxandrolone, stanozolol (Winstrol), and dromostanolone (Masteron) are AAS which do not convert to estrogen at all and which avoid the problem entirely.

For those compounds which do convert to estrogen, the problems experienced include increased inhibition of natural hormone production (which however is not mediated only by the estrogen receptor, so the problem is not entirely solved by blocking estrogen), possible gynecomastia (abnormal development of breast tissue), liver problems, and water retention. We have previously discussed anti-estrogenic agents.

The other main area of concern with safety of these drugs is hepatotoxicity of oral anabolics. Primobolan oral does not have this problem, but on the other hand, is essentially useless for a male bodybuilder at 5 mg/tab. At least 100 mg/day would be needed even for mild effect, and this simply would be cost prohibitive. Oxandrolone has minimal liver toxicity, but is not known for greatly increasing gains, and is expensive. Stanozolol has some toxicity and is not particularly effective. This leaves methandrostenolone (Dianabol) and oxymetholone (Anadrol.) Dianabol is rather mild in its liver toxicity, at least if it is not used for many weeks consecutively. Anadrol can make some users feel rather ill rather quickly. In my opinion, if Dianabol will do the job, and it will in most cases, it is the better drug of the two. If nothing else, it is simply more pleasant for the user.

Cycle Planning

The next thing to be considered, after "What drug?" and "What dose?" is how long the drug should be used, or what pattern should be used if the drugs are varied.

Now again, we must consider the goals of the user. If we are speaking of an IFBB pro it simply is not realistic in today's age to suggest that he should ever come off the drugs at all while competing. Others are not taking time off, and he would fall behind if he did choose to take off weeks and allow his system to return to normal periodically. Therefore, I am addressing here the concerns of the more average athlete who does not desire to be on drugs perpetually, and desires to maintain most of his gains while off drugs.

If gains are to be retained, losses at the end of the cycle must be avoided. Such losses occur if the natural hormonal axis, involving the hypothalamus, pituitary, and testes, is not producing normal levels of testosterone by the time that anabolic drugs are no longer providing significant levels to the system.

Incidentally, inhibition of each of these organs is somewhat independent of the others, and different factors are involved for each. We'll look at those issues in a future article.

The risk factors for inhibition are principally length of the cycle, choice of AAS, dosage of AAS, and in the case of orals, dosage pattern of AAS.

Very simply, the longer the cycle, the greater the chance of recovery problems. And in calculating the cycle length, one must take into account the half life of the drug, and the time required for levels to injected drug to fall below inhibitory levels. This will be several half lives. Thus, some people speak of 2 week cycles using Sustanon, with 2 weeks "off," which is then repeated. But they are incorrect in believing that they are doing 2 week cycles. Because substantial and inhibitory amounts of Sustanon will remain in the system during the "off" weeks, there is no recovery. If a person strings 4 of these cycles together, for example, he will have been on steroids for 16 weeks and may well have a difficult time recovering natural testosterone production afterwards. Thus, this is no solution.

The same type of scheme, however, can be quite successful with testosterone propionate with use of antiestrogens, as reported for example by Alexander Filippidis in a case study. With this shorter acting drug, there is actual time off between cycles.

Single short cycles, with many weeks allowed before beginning another new cycle, don't seem so efficient. Usually, real strength gains don't begin coming until the third week or so. While muscular weight may be gained in the first two weeks, it seems that the body is also adapting itself in a manner which will make growth very efficient in the next few weeks: or rather it would, if AAS were still available. Thus, I can't recommend doing isolated cycles which are shorter than four weeks at the minimum, and really five or six

weeks is probably more reasonable. Only in the case of short acting drugs, with very frequent cycles, are two or three week cycles a good idea in my opinion.

While it makes little sense to cut a stand-alone cycle too short, while the body is still ready to gain rapidly, on the other hand, heavy use beyond say 10 weeks becomes fairly likely to result in recovery problems. Furthermore, after the body has already grown a good deal and has been growing for many weeks, it is less ready to grow more. Thus, long cycles are inefficient in that regard, and furthermore are likely to result in greater losses after the cycle. Perhaps 6 weeks of heavy use and two to four weeks of light use is approximately optimal for conservative users.

The choice of AAS is quite critical towards the end of the cycle, so far as inhibition is concerned, but the inhibition issue is not so vital at the beginning. In other words, if one hits the system heavily at the beginning, but then lightly at the end, recovery will be better than if the reverse strategy were employed.

Primobolan, while not an exceptionally strong anabolic per milligram, seems to have a better ratio of anabolic to inhibitory activity than any other steroid, and is my recommendation as the injectable to use in the last weeks of a cycle. It is not absolutely clear though that this is an intrinsic property of Primobolan. It may be due to the fact that Primobolan does not convert to estrogen, and perhaps (this is speculation) low dose trenbolone might give an equally favorable anabolic/inhibitory ratio.

Dosage for this use is somewhat less clear. Some have made excellent recoveries on a gram of Primobolan per week. In the US, however, such use would be quite expensive. In general, though, I don't know if most people will recover well with that dose. 400 mg/week is still sufficient to saturate the androgen receptors (ARs) and is a more conservative approach for the last weeks of a cycle.

Where oral anabolics are concerned, once-a-day dosing results in much less inhibition than divided doses. It's unknown what time of day is best, but morning has been used successfully, and makes sense since that timing will result in little drug being in the system at night and early morning, when LH and natural testosterone production are highest. Thus, switching to once a day dosing in the last few weeks would make sense.

Our goal throughout the cycle as a whole, however, cannot simply be to minimize inhibition. If it were, the answer would be simply to take no AAS at all, or to use very little.

In the early phases of the cycle, inhibition must simply be accepted if serious gains are desired. This is not because inhibition itself in any way leads to gains, but simply because there is inhibition mediated by the androgen receptor, and therefore high levels of androgen will cause some inhibition. And as long as inhibition is occurring anyway, gains may as well be as much as possible. I see no point in half-measures. Either be gaining as much as possible, or be setting yourself up for recovery while still making some decent gains or at least maintaining gains.

For the early part of the cycle, the inhibitory properties of the AAS used are of less importance than the mass-gaining properties.

Two anabolics reign supreme: testosterone and trenbolone (which is found in Parabolan or in illicit injectable preparations of Finaplix.) These AAS appear more effective for mass building than any other injectables.

They may be stacked to advantage: since one is unlikely to be able to afford or to obtain large amounts of Parabolan, it is worthwhile to add testosterone in order to obtain a higher total dose and greater results. Furthermore, there may be a synergistic effect. However, trenbolone itself, particularly in combination with Dianabol, can give excellent results. Oral AAS add their own benefits, not because of binding to different receptors, but probably because of their direct action on the liver, which produces various growth factors.

What about other injectables?

I see little point in stacking weaker injectables such as Deca or Primobolan in the heavy phase of the cycle. While on the one hand they probably won't hurt – if they bind to the AR, they will give essentially the same action as testosterone – if the phase is heavy there is already enough AAS to saturate the receptors. There is no benefit there.

And there is little benefit from any possible non-AR-mediated activity, since these drugs do not seem to have much if any such effect. Nor can they act to reduce the side effects of the heavier anabolics. So there is little point to using them in the heavy phase of the cycle.

Side effects of testosterone are the main reason why people have been interested in weaker drugs such as Deca. However, with an effective aromatase inhibitor such as Cytadren at 250 mg/day, stacked with an effective estrogen receptor antagonist such as Clomid at 50-100 mg/day, testosterone becomes comparable to Deca in terms of side effects for equally effective doses of drug.

Some have found that Proscar acts to minimize effects of testosterone use on skin and hair. The objection that reduced conversion to DHT might reduce muscular growth may have some validity. This might be true either because of loss of DHT activity on nervous tissue, or because of possible loss of non-AR-mediated effects of androstanediol, a DHT metabolite, or an indirect effect not occurring in muscle tissue itself. DHT itself is not an effective anabolic for muscle tissue.

If one chooses to use Proscar to minimize risk of hair loss, I would suggest topical use to the scalp, or if used orally, certainly not in excess of the recommended dose for medically-indicated use.

Recovery

There is one side effect cannot be blocked: if one uses heavy doses of testosterone and/or trenbolone for months, and then ends the cycle, losses of muscle will occur because of poor recovery. LH production will be low, and because it has been low for some time, very often it may take some considerable time for the pituitary to again produce normal levels. Furthermore, testicular atrophy may have occurred, although such can be avoided with occasional use of hCG during the heavy phase of the cycle.

Because of recovery problems, it is wise to limit the heavy phase to 5-8 weeks, and then switch to Primobolan for the last several weeks of the cycle, beginning two weeks after the last injection of long acting ester. Once a day dosing of orals might be concurrent with this.

If long acting esters were used, then the existing drug from the heavy phase will have significant anabolic effectiveness for 2-3 weeks after injection, depending on dose, and thus no injectables would need to be used in those weeks. After that point, if Primobolan is not available, one might wish to continue with once-a-day dosing of orals, very low dose (100 mg/week) testosterone with use of antiestrogens, or even perhaps use of androdiol or norandrodiol. A balance must be struck, however: there is a middle ground that we do not want to be in. There is a range where there is still some anabolic support yet there is fairly little inhibitory effect, but past this range, there still is not great anabolic effect, but there is substantial inhibition. One does not want to spend more time than necessary in this middle ground, but pass through it relatively quickly. Once in the light phase, the dose must remain low enough to allow recovery of natural hormone production to occur.

Clomid use should continue until the user is confident that natural testosterone levels have returned to normal.

Ultimately, there cannot be one answer for everyone. Different users will have different needs. The above is generally good advice for reasonably conservative bodybuilders who wish substantial results. Those desiring either more moderate or more extreme results would need to adjust their plans accordingly.

Antiestrogens

Because of their ability to reduce risk of gynecomastia (abnormal growth of breast tissue in males) and enhance recovery of natural testosterone production after a cycle, use of antiestrogens such as aminoglutethimide (Cytadren) and clomiphene (Clomid) has become popular in bodybuilding. Antiestrogens also can reduce bloating associated with

anabolic/androgenic steroid use, and may avoid health risks associated with elevated estrogen levels. Medically, the drugs are used not only for treatment of breast cancer but also for improvement of fertility in both men and women, and occasionally for increasing testosterone levels in men such as endurance athletes with low testosterone. There are two categories of antiestrogens: aromatase inhibitors and receptor blockers. Both shall be considered here.

Estrogens

As with androgens, where any hormone that has the activity of testosterone is an androgen and therefore all anabolic steroids are androgens, any hormone that has the activity of estradiol, the principal female sex hormone, is an estrogen. The most active natural estrogens in humans are estradiol and estrone.

These hormones are related to each other rather similarly to how the andro prohormones are related to each other. Just as androdiol has a hydroxy (or –ol) group at both the 3- and 17- positions, estradiol likewise has a hydroxy group at those positions. Estrone, like androstenedione, has keto (or –one, pronounced "oan") groups at those positions.

Estradiol is the most potent (effective per milligram) of the natural estrogens. It is produced either from testosterone via the aromatase enzyme, or from estrone via the estrogenic 17b-HSD enzyme.

Estrone is less potent, but all this means is that one needs more of it to accomplish the same job. It is produced either from androstenedione via aromatase, or from estradiol via the same 17b-HSD enzyme working in reverse.

From the standpoint of the bodybuilder using anabolic/androgenic steroids (AAS), if nothing is done about the situation, high estrogen levels can cause gynecomastia, will inhibit natural testosterone production, and will cause bloating. High estrogen levels also make it more difficult to lose fat, and tend to cause female pattern fat distribution even in males.

Estradiol also has carcinogenic metabolites, and a liver problem sometimes associated with AAS use, hepatic cholestasis, is caused not by androgen but by an estrogen metabolite.

It is also not unusual for bodybuilders to feel poorly on beginning a cycle of high dose testosterone without antiestrogens, and for this reason many have advocated starting with a low dose and building up. However, I strongly suspect that the real problem is estrogenic effect on mood, and the problem can be avoided with use of an aromatase inhibitor.

Aromatizable steroids

Though most bodybuilders feel they know which steroids aromatize and which do not, sometimes the beliefs are in error. This is because progestogenic activity (activity like that of progesterone, another female hormone) is easily mistaken for estrogenic activity. Both hormones can cause bloating, and both can cause gyno. So AAS which are capable of activating not only the androgen receptor but also the progesterone receptor are often mistakenly assumed to aromatize. (Note: these androgens do not "convert to progesterone" but rather are themselves, without any change needed, able to act on that receptor.)

Nandrolone is proven to be a progestin. This fact is of clear importance in bodybuilding, because while moderate Deca-only use actually lowers estrogen levels as a consequence of reducing natural testosterone levels and thus allowing the aromatase enzyme less substrate to work with, Deca nonetheless can cause gyno in some individuals. Furthermore, just as progesterone will to a point increase sex drive in women, and then often decrease it as levels get too high, high levels of progestogenic steroids can kill sex drive in male bodybuilders, though there is a great deal of individual variability as to what is too much.

Incidentally, this progestogenic activity also inhibits LH production, and contrary to common belief, even small amounts of Deca are quite inhibitory, approximately as much so as the same amount of testosterone.

What relevance does this have to an article on antiestrogens? Well, antiestrogens can do nothing about these side effects of Deca.

The same appears to be true of oxymetholone (Anadrol) and of norethandrolone (Nilevar).

Methenolone (Primobolan), stanozolol (Winstrol), dromostanolone (Masteron), oxandrolone (Anavar), mesterolone (Proviron), stenbolone (Anatrofin), trenbolone, and DHT do not aromatize, and thus, antiestrogens are not relevant to these AAS either.

The steroids where aromatization is of particular concern are testosterone, methandrostenolone (Dianabol), boldenone (Equipoise), and to some extent fluoxymesterone (Halotestin). However the latter is usually used in doses low enough that aromatization is not an issue.

Among the prohormones, androstenedione is the principal offender with regard to aromatization, being readily converted to estrone. With androdiol, only that small portion which converts to testosterone can be converted further to estradiol, and that will occur only in the same percentage that other testosterone converts to estradiol.

Norandrodiol cannot convert directly to estrogen, and even after conversion to nandrolone is not readily converted to estrogen.

Norandrostenedione can be converted to estrone by aromatase, but is a very poor substrate for that enzyme. It can actually act as a competitive inhibitor, blocking better substrates such as androstenedione or testosterone. It is possible then, though unproven, that norandrostenedione might have some value as an aromatase inhibitor in bodybuilding. I do think, however, that the pharmaceuticals designed for the purpose should be assumed to be better choices.

Aromatase inhibitors

The most commonly used aromatase inhibitor in bodybuilding is aminoglutethimide (Cytadren). This drug also inhibits an enzyme (desmolase) necessary for synthesis of cortisol, but fortunately, aromatase can be inhibited with levels of drug that cause only limited inhibition of desmolase.

Contrary to popular belief, it is generally not desirable to inhibit cortisol production. Doing so will likely lead to joint problems, and furthermore once the inhibition ends, the price of above-normal cortisol production must usually be paid.

For an average male, a dose of 250 mg/day (one tablet) appears optimal. The half-life is 8 hours, so the drug is better taken in divided doses. The best plan seems to be to take half a tablet on arising, and quarter tabs six and twelve hours later. This keeps levels generally fairly constant, but allows a small drop in the hours shortly before arising, which is then compensated for by the higher dose on arising. With this scheme, inhibition of cortisol production is generally too low to be noticed, and generally there is no rebound effect on discontinuance. However it is not a bad idea nonetheless to taper off, first omitting the midday quarter tab dose for a few days, then omitting both quarter tab doses, then reducing the initial dose to one quarter tab, and then ending completely. A week is sufficient for the taper.

Some people suffer a degree of lethargy or sedation from aminoglutethimide, even at this low dose, but most do not.

Anastrozole (Arimidex) is a superior aromatase inhibitor which does not have the above side effects. It is, however, very expensive. With moderate doses of testosterone it seems that 1 mg/day is sufficient, and some have claimed half a tab to be sufficient. I do not have blood test data to verify that, however.

Receptor blockers

Clomiphene (Clomid) and tamoxifen (Nolvadex) are the most popular drugs of this class. They are more precisely referred to as "selective estrogen receptor modulators." This is because their mode of action is not so simple as merely blocking the estrogen receptor.

Estrogen receptors require not only hormone but also activation of regions of the receptor called AF-1 and AF-2. AF-1, to be activated, requires phosphorylation, while AF-2 can be activated by any of a number of cofactors, such as IGF-1.

As it happens, clomiphene and tamoxifen are estrogen receptor antagonists (blockers) in cells that depend on activation of the AF-2 region, while in cells which activate AF-1, these compounds are estrogens.

In some cells these drugs activate one of the types of estrogen receptor (ERα) but are antagonists of the other type (ERβ).

The result is that these compounds are antiestrogenic in breast tissue, fat tissue, and in the hypothalamus, which is what we want in bodybuilding, but are estrogenic in bone tissue and with respect to favorable effect on blood lipid profile, both of which are, again, desirable. They also appear to have some estrogenic effect on mood, though this may be in only parts of the brain (the matter is not studied.)

Cyclofenil is a similar drug to the above two. Clomiphene will do everything that the other two will do, but for some unknown reason, has been found more effective than tamoxifen both medically and in bodybuilding for increasing LH production.

Raloxifene (Evista) is a new selective estrogen receptor modulator that, for women, has the advantage of being an antiestrogen in the uterus, whereas clomiphene and tamoxifen are estrogens in that tissue. For this reason, the latter two drugs can promote uterine cancer, while raloxifene actually should help prevent it, and is therefore a superior drug for women. It is not known how effective it may be in increasing LH production.

While on high dose androgens it is impossible to maintain LH production in any case, and clomiphene can do no good in that regard. As androgen levels return to normal, however, a dose of 50 mg/day of clomiphene if estrogen levels are reasonable, or 100 mg/day if estrogen levels are high, is usually effective in restoring natural testosterone production.

Because the drug has a long half-life, when one takes 50 mg/day the amount in the system is not only the 50 mg just taken, but also approximately another 250 mg from previous days. Thus, to immediately arrive at the therapeutic level, one would take 300 mg (50 mg six times) on the first day, and then continue with 50 mg/day.

A small percentage of individuals suffer vision problems from use of clomiphene, which is generally reversible upon discontinuance. These persons, of course, should not use the drug after discovering the problem.

It also must be pointed out that these are prescription drugs, and should be obtained and used only by precription with medical advice, though the selective estrogen receptor modulators have excellent safety records.

After a cycle, it is reasonable to continue clomiphene use until at least four weeks after the last injection of long acting ester, or at least two weeks after the last use of an oral, or until natural testosterone production is clearly back to normal, whichever comes last.

Conclusion

Other than acne and accelerated hair loss, the two most common problems of AAS use are gynecomastia and difficulty in recovering natural testosterone production. Antiestrogenic drugs can effectively address both problems and are safe for most individuals. Ideally, if aromatizable drugs are used, the problem is corrected at the source by limiting production of estrogen by using an aromatase inhibitor. However, it is also effective to use a selective estrogen receptor modulator such as Clomid. The latter drug is also of particular use in helping to restore natural testosterone production after a cycle.

Inhibition and Recovery of Natural Testosterone Production

One of the most significant side effects of anabolic/androgenic steroid (AAS) use is inhibition of natural testosterone production. There is no way to entirely avoid the problem, but there are ways to minimize the problem and recover natural testosterone levels reasonably quickly after a cycle. In this article, we will look at the problem of inhibition, its causes, and the best solutions currently known.

The Causes of Inhibition

Elevated hormone levels, in general, *will* cause inhibition of natural testosterone production. Many bodybuilders have come to believe that elevated estrogen levels alone are the sole cause of inhibition, and believe that by blocking estrogen, they can block inhibition.

This is not true. For example, consider the results seen in the second 2-on / 4-off cycle case study reported on Meso-Rx where Jim used 50 mg/day of trenbolone acetate, which does not aromatize, 50 mg/day of Dianabol, which does aromatize, with 250 mg/day of Cytadren as an aromatase inhibitor and 50 mg/day Clomid as an estrogen receptor blocker. His estrogen levels remained in the normal range, though elevated from baseline, since apparently the Cytadren was not sufficient to block aromatization completely. The Clomid should easily have been able to overcome normal estrogen levels, and so if the estrogen-only theory of inhibition were correct, Jim should have been suffering no inhibition. But the fact is, his testosterone levels dropped to only 1/10 his baseline value.

Estrogen alone was not the cause of his inhibition. It could not have been the cause of any of it, given the normal levels and the Clomid use.

So much for the estrogen-only theory of inhibition that has been claimed by other writers. That isn't to say, though, that estrogen is not *also* inhibitory: it is.

What then besides estrogen can cause inhibition? DHT, which does not aromatize, has been extensively shown to cause inhibition of testosterone production. Androgen alone, then, is sufficient to cause inhibition. In Jim's case, androgen use was moderately heavy, and androgen alone would seem the cause of the inhibition.

Progesterone is another hormone that can cause inhibition, when used long-term. Paradoxically, in the short term it can be stimulatory. Other relevant factors include beta agonists, opiates, melatonin, prolactin, and probably other compounds. With the exception of beta agonists (e.g. ephedrine and Clenbuterol) and opiates (natural endorphins on the one hand being inhibitory, and Nubain blocking such inhibition) manipulation of these would not seem useful in bodybuilding.

The Hypothalamic/Pituitary/Testicular Axis (HPTA)

To understand inhibition of testosterone production, we need to know first how it is produced and how production is controlled. The broad general picture is that the hypothalamus receives a variety of inputs, for example, levels of various hormones, and decides whether or not more sex hormones should be produced. If the inputs are high, for example, high estrogen or high androgen or both, then it decides that little or no sex hormones should now be produced, but if all inputs are low, then it may decide that more sex hormones should be produced. It seems that the hypothalamus doesn't respond only to current hormone levels, but also to the past history of hormone levels.

The hypothalamus itself cannot produce any sex hormones – instead it produces LHRH, or *luteinizing hormone (LH) releasing hormone,* also called GnRH *(gonadotropin releasing hormone.)* This then stimulates the pituitary gland.

The pituitary uses the amount of LHRH as one of its signals in deciding how much LH it should produce. Proper response depends on having sufficient receptors for LHRH. These receptors must be activated for LH to be produced. The pituitary also uses sex hormone levels, both current and the past history, in deciding how much LH to produce. Some aspects of the pituitary's behavior are peculiar. For example, too much LHRH results in the pituitary downregulating LHRH receptors, with the result that very high LHRH production, which one would think should result in high testosterone production, actually lowers testosterone production. Another oddity is that while high estrogen levels inhibit the pituitary, still some estrogen is required to maintain a high number of LHRH receptors. So both very low and high levels of estrogen can inhibit LH production.

LH produced by the pituitary then stimulates the testicles to produce testosterone. Here, the amount of LH is the main factor, and high levels of sex hormones do not seem to cause inhibition at this level.

Inhibition From AAS Cycles

Because high androgen levels sustained around the clock *will* cause inhibition, traditional cycles simply cannot avoid inhibition of LH production while on cycle. There are three ways to avoid it:

- Avoid having high androgen levels around the clock. This can be done, for example, by using oral AAS only in the morning, with the last dose being approximately at noontime. Even 100 mg/day Dianabol can be used in this fashion with little inhibition. The problem with this approach is that gains are not very good compared to what is seen when high androgen levels are sustained around the clock.
- Use an amount and kind of AAS that is low enough to avoid much inhibition. Primobolan at 200-400 mg/week may achieve this effect. Again, gains will be compromised compared to a more substantial cycle. Testosterone esters and Deca are substantially inhibitory even at 100 mg/week so using a low dose of these drugs will simply result in both inhibition and poor gains.
- In principle, one could use an antiandrogen, but this would totally defeat the purpose of the cycle.

Where AAS doses are sufficient for good gains, an interesting pattern is seen. For the first two weeks of the cycle, only the hypothalamus is inhibited, and it produces much less LHRH as a result of the high levels of sex hormones it senses. The pituitary is not inhibited at all: in fact, it is actually sensitized, and will respond to LHRH (if any is provided) even moreso than normally. After two weeks however, the pituitary also becomes inhibited, and even if LHRH is provided, the pituitary will produce little or no LH. This then is a deeper type of inhibition. After this point, there seems to be no definite further "switching point" where inhibition again becomes deeper and harder to reverse. As a general rule, I would say that there seems to be little difference between using AAS for 3 weeks vs. 8 weeks: recovery is about the same either way. Between 8 and 12 weeks, it becomes more and more likely that recovery will be difficult and slow, though even at 12 weeks it is common for recovery to not be too problematic, taking only a few weeks. Cycles past 12 weeks seem much more likely to cause substantial problems with recovery. In the hundreds of consultations I have done for people with recovery problems, very few (I can recall two) were for very short cycles such as 6 weeks, while most were for usages of 12 weeks straight or more.

I do not know what changes take place in the hypothalamus and pituitary over a long period of time that result in this problem, but it certainly is true that long-term inhibition makes recovery more difficult on average. I suspect the problem may have to do with

change in the "clock" that regulates the pulse rate of LHRH secretion, but I am not sure that that is so.

Drugs of Use With Regard to Inhibition

Cytadren: This drug can be used to reduce conversion of testosterone, Dianabol, and Equipoise (not an exclusive list of aromatizable AAS, but the main ones) to estrogen. Some feel that when estrogen levels are kept under control during the cycle, recovery is faster after the cycle is over, though that is not proven. It is a good idea though. And if testosterone esters were used prior to ending the cycle, some levels of these will remain for weeks, and continued use of Cytadren will help prevent conversion to estrogen, and thereby reduce inhibition. The best dosing pattern, in my opinion, is to take ½ tab (125 mg) on arising, and then ¼ tab at six and 12 hours later. Use of more Cytadren than this, or a different pattern, may lead to an adverse effect on cortisol production, with subsequent cortisol rebound after discontinuing the drug. Some individuals suffer some lethargy (feeling of tiredness and laziness, or sleepiness) from Cytadren, but that is uncommon at this dose.

Arimidex: This accomplishes the same purposes as Cytadren but without the possible side effects mentioned above. It is however far more expensive. A typical dose is 1 mg./day. The timing of the dosage does not matter, since the drug has a long half-life.

Clomid: After a cycle is over, Clomid at 50 mg/day is usually very effective in restoring natural testosterone production. It acts by blocking estrogen receptors at the hypothalamus and pituitary. If androgen levels are not elevated, this is enough to cause production of at least normal amounts of LH, or often more LH than normal. During the cycle Clomid cannot prevent inhibition, though some think using it during the cycle will allow a faster recovery afterwards. That is not proven though. If nothing else, though, it is useful as an antigyno/antibloating agent during the cycle.

Nolvadex: This works in the same manner as Clomid, but not nearly so well with regard to reversing inhibition. It is better to use this only as an anti-gyno/antibloating agent, if at all. If Clomid is used, there is no need for Nolvadex.

HCG: This does nothing with regard to inhibition of the hypothalamus and pituitary. Rather it acts like LH, and causes the testicles to produce testosterone just as if LH were present. It is useful then for avoiding testicular atrophy during the cycle. The best dosing method is to use small amounts frequently: 500 IU per day is sufficient, and 1000 IU may optionally be used. The amount may be given as a single daily dose or divided into two doses. Administration may be intramuscular or subcutaneous. More is not better: too much HCG can result in downregulation of the LH receptors in the testes, and is therefore counterproductive. Overdosing of HCG can also result in gynecomastia.

Ephedrine/clenbuterol: It is possible that the beta agonist activities of these drugs may assist in recovery. Personally, I do recommend the use of ephedrine post-cycle to those who can use it. Clenbuterol has the same effect but acts around the clock, having a longer half life, and allowing a higher effective dose (amount times potency) due to having less relative effect on beta receptors in the heart. I am not sure that clenbuterol has any better effect with regard to recovery though.

Oral AAS: These do not assist recovery of natural testosterone production, but if used only in the morning, can help sustain muscle mass while in the recovery phase, with little or no adverse effect on recovery.

Tribulus: If this is of benefit, I have not been able to observe it myself. I have only tried the Tribestan brand, but this is the brand that earned tribulus its reputation.

Melatonin: While disrupted sleep patterns definitely inhibit recovery, I have seen no evidence that taking melatonin at night speeds recovery. It is useful though for those who have allowed their sleep patterns to be disrupted and who wish to reset their natural clocks.

General Recommendations

Pharmaceutical drugs should of course not be self-prescribed: the following are simply recommendations of what works well, not of what to do without physician's advice. Enough said.

The best cycle plans are either brief two week cycles with short acting drugs, which allow a very fast recovery (less than one week) or cycle of approximately 6-10 weeks, which usually allow reasonable recovery and allow quite a bit of time to make gains. Cycles in the 3-5 week range are less efficient because they combine the disadvantage of relatively little time gaining with the disadvantage of slower recovery.

If a cycle lasts 8 weeks or longer, I think it is best to use HCG during the cycle if possible, as described above. HCG should not be used during the recovery itself since it will increase androgen and estrogen levels, which will be inhibitory to the hypothalamus and pituitary.

Clomid use should begin, if it was not used during the cycle, as soon as androgen levels drop enough that recovery becomes possible. This would be about two weeks after the last injection of long acting steroid esters, assuming reasonable doses such as 500 mg/week. Clomid use should start with 300 mg on the first day (50 mg six times) to quickly get blood levels as high as needed, and then maintained with 50 mg/day. This is needed because of the half-life of the drug. It should be continued until one is sure that natural testosterone production is back and testicle size is returned to normal, with the exception that if use has been more than about 6 weeks, one might try dropping it for a

few weeks to see what happens. If no further improvement occurs, then Clomid would be resumed. It has been studied medically for long-term use and found safe for periods of at least a year. However, a small percentage of users develop vision problems from Clomid, which are generally reversible upon discontinuing the drug. So if you have this problem, certainly the drug should be discontinued.

If aromatizable injectables were used, an antiaromatase would be useful for 3 weeks or so after the last injection, or 4 weeks if dosage was high (a gram per week or more.)

Lastly, ephedrine seems to be of some help. The same dose as used for dieting (e.g. 25 mg three times per day) seems quite sufficient.

Long term inhibition can potentially be a serious side-effect of AAS use, and this risk should be minimized by avoiding excessively long cycles. This really does not compromise gains greatly, since the body cannot grow rapidly week in, week out, 52 weeks per year anyway. And even moderate post-cycle inhibition is something we wish to minimize, since it is frustrating to lose much of one's gains in the first few weeks after a cycle as a result of low natural testosterone and no AAS being used. The advice given above is generally successful in minimizing such losses, and I hope you will find it useful.

Pharmacological Differences Between Anabolic-Androgenic Steroids (AAS)

One rather key issue to usage of anabolic/androgenic steroids (AAS) is how one chooses which to use, or which combination to use, and indeed, why combinations might be superior to comparable amounts of single steroids. The issue of combining AAS for most efficient muscle gain is one that has been entirely neglected in the medical literature, since acquisition of muscle is not considered of therapeutic necessity, and observations by bodybuilders have unfortunately generally not been made in a systematic manner. I cannot yet give definitive and complete answers on this matter, but some things are clear at this point, and general support for the principle of synergy can be found in some scientific studies.

Pharmacology in the Simplest Case

First, let us consider the case of the simplest kind of drug. This drug would act in only one way, and would do so by binding to a receptor and activating it. The amount of activity performed by that type of receptor would be directly proportional to the number of receptors that bound the drug. Nothing else of any kind would be going on with this drug.

There might also be similar drugs which worked the exact same way, binding to the same receptor. The only ways in which these drugs could differ from the practical point of view are in pharmacokinetics (how fast each drug enters and clears the body) and how *potent* each drug is. The latter term is one that may easily be misunderstood due to common usage differing from scientific usage. Potency refers to how little of a drug is required to give a defined amount of effect. For example, if one may obtain the desired therapeutic effect in 50% of subjects with 1 mg/day of Drug A or 100 mg/day of Drug B, then Drug A is 100 times more potent.

This does not mean that Drug A is necessarily better! One can get the same effect from Drug B simply by using 100 times as much. It might be the case that Drug B might be preferable despite the higher required dose: for example, if Drug A leaves the body too quickly or too slowly, or has more toxicity for the same therapeutic effect. It means only that in comparing the drugs, to compare them equally, one must compare the effects of 1 unit of Drug A to 100 unit of Drug B.

To understand this a little more, unfortunately we have to use a little math. One could skip over the math if desired and just look at the conclusions which follow fairly easily from the numbers calculated.

Drugs and receptors interact with each other according to a simple equation:

$$K_d = \frac{(\text{conc. of drug})\,(\text{conc. receptor})}{(\text{conc. of drug} \leftrightarrow \text{receptor})}$$

where (conc. of drug $\leftrightarrow$ receptor) is the concentration or amount per volume of receptors that have drug bound to them, and (conc. of drug) and (conc. of receptor) refer to the concentrations of free drug and receptor respectively.

This number K_d is a constant (always the same) for any given drug, but will vary between drugs of different potencies. This fact allows us to calculate the percentage of receptors occupied if we know K_d and the amount of drug.

K_d will be expressed in units of concentration, for example, 1 nanogram per liter. More potent drugs have lower K_d values. In our comparison of Drugs A and B where A was 100 times more potent, if Drug A had a K_d value with the receptor of 1 ng/L, then drug B would have a K_d of 100 ng/L: you would need 100 times more of Drug B to get the same effect.

What would happen therapeutically if you "stacked" Drug A and Drug B?

You can play with the math and you will find that using blends of A and B, where one keeps in mind that B is 100 times less potent and therefore uses 100 mg of it for each unit of A it replaces, that one gets the exact same result regardless of the stacking. Let’s say that Drug A comes in 1 mg tablets and Drug B comes in 100 mg tablets. Each tablet

therefore gives the same effect. In the case of the simplest type of drug such as these two drugs, the effect is identical whether one uses 10 tabs of A, 10 tabs of B, or 5 tabs of each. The same number of receptors are occupied regardless and the effect is the same.

Therefore, stacking these drugs makes about as much sense as stacking two brands of aspirin or two brands of coffee. It is okay if one happens to have both available, but there is no reason to go out and buy the second brand in the hopes that stacking it will give more of a caffeine buzz, or more pain relief.

The mixing might make sense if there were a pharmacokinetic difference: perhaps one of the brands of aspirin is time-released and you want both an instant hit for immediate pain relief as well as sustained action. (The sustained action though could be obtained with only the regular brand, simply by taking small amounts frequently.)

Application to AAS

Now the obvious question here is, Is the same type of drug response true with AAS, or are more complex things going on? Let's say that, used alone, the same effect is obtained from 1 "Deca-unit" of Deca (let's say that a Deca-unit is 400 mg) or from 1 "Dianabol-unit" of Dianabol (let's say that this is 280 mg/week in divided doses every day). If these drugs were as simple in action as Drugs A and B, then the math says that the same result will be obtained regardless of whether one uses one "Deca-unit" of Deca per week, one "Dianabol-unit" of Dianabol per week, or half a unit of each respectively in a stack.

This however is not what happens. Using half a Deca-unit and half a Dianabol-unit per week (say 200 mg/week Deca and 20 mg/day Dianabol) gives better gains than using one unit of either alone. This effect is called synergy and results when there is more than one mechanism of action. The above math remains correct for any given receptor but this is saying that there are more things going on in the body than simply binding to one receptor.

Aside from this and other practical but well-confirmed observations, there is scientific evidence that this is indeed the case.

Scientific Evidence for Multiple Modes of Action

The first thing to consider is whether or not a single mode of action is sufficient to explain all results, as with the simplest case described for Drugs A and B, or whether data is in conflict with such a model.

The equation given earlier allows one, given a measured K_d value, to calculate what percentage of receptors is occupied for a given concentration of drug.

The K_d value for testosterone and the androgen receptor (AR) actually is not known with great precision for humans, but is approximately .44 nmol/L.[1] Free testosterone levels in normal men average approximately .07 nmol/L.[2,3,4]

Contrary to previous statements made by me (although those statements had been made in the scientific literature) this indicates that normal testosterone levels are not sufficient to saturate the AR. The equation given shows that with these values for free testosterone (T_f) and for K_d, one would expect only 14% of ARs to be occupied at any time. Increasing T_f by ten times would improve this to 61% occupancy, which still is not saturated. Increasing twenty times would yield further improvement to 76%. Perhaps this correlates well with the observation that gains improve markedly relative to low dose as one increases amount of testosterone used to 1 gram per week, but going to 2 grams per week offers only a modest further increase.

These results surprise me and are definitely contrary to accepted wisdom. I can only speculate at the moment that those who were trying to determine whether or not receptors are saturated made the mistake of performing the calculation with total testosterone levels instead of T_f. Doing so would lead to that conclusion but is an incorrect method.

I had been going to argue as I had previously that the dose response curve, which extends at least to the 1 gram per week level,[5] indicates that there must be more than one mechanism of action, since response increases even past the point of saturation. However these calculations just performed indicate that the dose response curve, through the range that has been studied, is in accord with known values for K_d. This doesn't prove that there is only one mechanism, but just that one mechanism is not disproven by the dose response curve.

Is there other evidence for multiple mechanisms?

Yes.

First, there are indisputably molecular targets that are not ARs within some cells which bind androgen and give pharmacological response to androgen. These targets may well have (and in some cases are shown to have) quite different binding properties than the AR does. One AAS might be more potent than another at the AR, but less potent at this other target.

Now these targets are not well known or characterized at all, but there is compelling evidence for their existence. First, as discussed above, for any given target (or receptor) drugs acting only at that receptor will behave the same way and differ only in their potencies. Now if all AAS behaved the same way and differed only in their potencies, and had the same ratios of potency regardless of the activity being studied (whether in muscle or skin or nerves, etc.) then this would be consistent with there being only one target or receptor. However, if some AAS are effective in some activities but do nothing in others, while other AAS do have these other activities, then this can't all be occurring from the same receptor.

Most of the research in this area is rather far removed from bodybuilding, but the principles still apply. Biochemistry is usually much broader than any one specific cell being studied. (For example, most human biochemistry was actually learned originally by study of *E. coli* and with later research found to be identical in man.) Thus, while we may not care about ductal branching morphogenesis in the developing rat prostate, the fact that a peculiar biochemical mechanism of androgen response occurs here implies that such a mechanism may well exist in things we are interested in, such as bodybuilding. The possibility at least exists.

Speaking of ductal branching morphogenisis in the developing rat prostate,[6] here indeed different steroids behave differently. While to the AR testosterone is less potent than DHT, here the reverse relationship was found. Furthermore, methyltrienolone, which is a more potent agonist (activator) of the AR than is DHT, was no more effective than DHT in inducing ductal branching and was less effective than testosterone. This cannot be explained by assuming that aromatization of testosterone to estradiol contributed to the process, because 5α-androstan-3α,17β-diol (which cannot aromatize) was similarly potent. Thus, there is some target or receptor in these tissues which has different "preferences" (K_d values, and different rank order of potency) than the AR does. Could this also be the case for muscle growth? Perhaps.

Another example is found in the virilization of the mammary gland of female rats.[7] The same results are seen here as in the above example of the rat prostate. Testosterone (T) has more activity than DHT does, though at the AR that would not be so.

Differences also are seen in the male accessory glands of the rabbit and rat.[8] Testosterone propionate and DHT propionate were found to be equally potent in supporting growth and secretory activity of these glands, but the above-mentioned 5α-androstan-3α,17β-diol was considerably more potent than these in the prostate but completely ineffective in the epidydimis. Furthermore, use of an antiandrogen (AR blocker) did not affect the function of the epidydimis at all. Thus, the activity of testosterone and DHT in this tissue *is not via the AR.* Are there muscle-building activities that are not via the AR? If the mechanism exists in one tissue it probably does in others as well.

Here is an activity that is itself of more interest: regulation of lipolysis (fat release) in adipocytes (fat cells).[9] T, but not DHT, stimulated catecholamine-induced lipolysis. The findings indicated that T but not DHT induced upregulation of β-adrenergic receptors.

Use of an aromatase inhibitor did not change these results, so conversion to estrogen was not responsible for the difference. If this activity were via the AR, DHT would also have exhibited this effect. Clearly then, something is going on that is not via the AR.

Differential effects of different AAS on human fat cells have also been seen.[10] Oxandrolone was most effective in reducing subcutaneous abdominal fat and visceral fat in obese middle-aged men while weight did not change, as a result of muscle mass increase. Testosterone enanthate gave a small decrease in subcutaneous fat but a slight increase in visceral fat. Nandrolone decanoate also increased visceral fat while decreasing

subcutaneous fat. If these activities were via the AR, all three steroids should give the same effects, differing only in potency or the dosage required.

There are some interesting studies on sexual receptivity of female rats. Methyltestosterone, methandrostenolone (Dianabol), nandrolone decanoate, and stanozolol all interfered with sexual receptivity (a different result than seen in human bodybuilders) while testosterone propionate did not.[11]

In male rats,[12,13,14] differential activities are also seen. In intact (non-castrated) male rats, testosterone cypionate, nandrolone decanoate, and methandrostenolone (Dianabol) were all able to support male sexual behavior, while methyltestosterone, stanozolol (Winstrol), and oxymetholone eliminated male sexual behavior. Again, these results are different than are seen in human bodybuilders. Testosterone cypionate was able to maintain ejaculation in castrated rats, while oxymetholone (Anadrol) was barely able to do so, and stanozolol was unable to do so. This however might have to do with estrogenic activity – use of an aromatase inhibitor was not tried.

Oxandrolone was found incapable of supporting reproductive development in the young male rat.[15] Weight of testes, prostate gland, and seminal vesicles were all below controls, and Leydig cells were severely depleted. Again, it was not ruled out that reduced estrogen levels of the oxandrolone-treated animals might have been to blame, so this does not actually prove a non-AR-dependent mechanism for reproductive development. It does indicate that androgens other than testosterone combined with low estrogen levels can result in fertility problems in the rat, and therefore long-term use of nonaromatizing steroids might affect sperm count in the human as well.

Virilizing activities in female rat fetuses also showed a trend of potencies different from trends of binding affinities to the AR.[16] The specific test used was measurement of the abridgment of urovaginal septum length: admittedly not so directly relevant for female bodybuilders. The most active AAS was stanozolol, which was more active than methyltestosterone despite having much poor binding affinity to the AR than that steroid.[17]

In Syrian hamster embryo cells, trenbolone, a more potent agonist of the AR than testosterone, was found unable to transform these cells while testosterone was effective.[26] This indicates that the mechanism cannot be simply via the AR.

The AR is not a membrane-associated receptor, but exists within the cell. However, receptors for testosterone have been found in the cell membranes of T cells. The activity of testosterone (increase of amounts of Ca^{++} within the cell) occurs within seconds (and therefore cannot be via interaction with DNA resulting in increased protein synthesis, since this is a slow process) and was not affected by an AR blocker.[18] This effect has also been seen in Sertoli cells.[19]

Androgen binding receptors have also been found in cell microsomes – these receptors cannot interact with DNA because of their location.[20,21,22] Stanozolol has been found to have activity in microsomes that testosterone does not.[23,24,25]

Lastly, while only stanozolol was tested and therefore we cannot know if there is differential activity between different steroids or not, stanozolol induced a type of skeletal muscle injury that was thought perhaps to stimulate growth, and to induce gene expression by an AR independent mechanism.[27] At last, a specific example related to muscle that shows that not all activity is via the AR alone.

We might also speculate that AR upregulation (which has been demonstrated to occur under some conditions (see Androgen Receptor Regulation) is probably not itself mediated by the AR. It would be an unstable mechanism to have the number of ARs increase as a result of increasing numbers of activated ARs. More likely there would be another mechanism.

We may also speculate that different AAS have different effects on nerves, and these effects (being rapid) are not mediated by the AR. E.g., fluoxymesterone, while it binds fairly poorly to the AR, is highly potent in stimulating aggression, and this activity occurs quickly.

Conclusion

What to do with this information? Unfortunately we cannot yet identify how many non-AR-mediated activities there may be. There are I think at least two: activity in microsomes and activities in nerves. There may be more. For example, differentiation of satellite cells of muscle into mature muscle cells might be a non-AR mediated activity.

The practical application of this is that one should not use only a steroid which is good at some things but not others. Examples of this would be Deca and Primobolan (good agonists of the AR but this is not sufficient to make them outstanding anabolics) and Anadrol and Dianabol, which are weaker agonists of the AR yet effective anabolics. Combining drugs of one type with the other is synergistic. It may also be that testosterone and trenbolone are synergistic – trenbolone is much more potent at the AR but (as seen with the Syrian hamster cells) testosterone has at least one activity that trenbolone does not. Winstrol has metabolic properties that testosterone lacks.

Is there a reason to use both Dianabol and Anadrol together? Does one have one non-AR mediated activity which the other lacks? I think not, although Anadrol does seem to have progestogenic activity which Dianabol does not. In any case I don't know anyone who likes to combine these drugs.

Right now I would say that all bases are covered with testosterone plus trenbolone plus (Dianabol or Anadrol) plus Winstrol. I am not sure that there is no overlap: perhaps the activities of testosterone are covered by the other three.

I hope that future careful observations of results obtained in bodybuilding will allow a more precise answer to this question in the future.

Anabolic Steroid Esters

Injectable anabolic steroids are usually available as *esters* of the parent drugs. Often, a drug in its original form may lack certain properties that are desired: for example, good solubility in oil or fat. There may be a part of the molecule to which one may add an additional chemical group to give the new molecule desired properties, but in such a way that over time in the body, the modification will be removed, restoring the parent drug. If the modified molecule is itself not active, needing to be converted back to the parent drug, then this is a *prodrug*. Anabolic steroids such as testosterone cypionate and nandrolone decanoate are prodrugs. Since esters of anabolic steroids are so often used in bodybuilding, in this article we will examine them closely.

At a particular position (#17) all anabolic steroids have a *hydroxy* group, consisting of an oxygen and hydrogen, represented by OH. This can be replaced by an ester group: for example, propionate ($OOCCH_2CH_3$). This results in improvement in solubility in oil and reduction of water solubility, both of which are useful for reasons later to be discussed.

How do esters differ in structure?

While quite an array of names exist and make the issue seem complicated, the main difference between different esters is simply the number of carbon atoms in the ester. Propionate, as shown above, has three carbons, whereas acetate has two, isobutyrate has four, enanthate has seven, cypionate has eight, and decanoate has ten. On occasion there are more unusual esters, such as cyclohexylmethylcarbonate (used in Parabolan) which has eight carbons and one more oxygen than the above esters do.

How do esters change the physical properties of steroids?

Testosterone, nandrolone, and other anabolic steroids have poor solubility in either water or oil. Esterifying them improves oil solubility. This enables useful dosages of perhaps 100 mg or more per cc. But the more carbons the ester has, the lower the water solubility becomes, and the higher the *partition coefficient* (ratio between lipid and water solubilities) becomes. If the partition coefficient is high, then at any moment a high

proportion of the prodrug is dissolved in oil or body fat, and only a small proportion is dissolved in water.

This is important. If testosterone itself is given in oil solution, it transfers too easily from oil to the water in the blood. The result is that an oil injection of testosterone gives a sudden spike in testosterone levels, which rapidly drops. Injections would be required at least twice per day, and perhaps even more often. Improving the oil solubility and decreasing the water solubility slows this transfer, and extends the half-life of the drug to several days or more.

The number of carbons also has a small effect in that it reduces the parent drug's proportion of the total weight. E.g., it would take 344 mg of testosterone propionate, or 401 mg of testosterone enanthate to give the same amount of testosterone as in 288 mg of testosterone suspension.

How are esters converted back to the parent drug?

The ester bond is fairly easily broken under the right conditions. If the molecule is dissolved in water, this can occur by a simple chemical reaction, yielding the parent drug and a *carboxylic acid.* For example, if the steroid used is testosterone propionate, testosterone and propionic acid are released. Carboxylic acids are safe and natural in the body in reasonable amounts. It should not be thought that these are strong acids because they are not: they are acids in the same sense that, e.g., Vitamin C or lactic acid are acids. Furthermore, the amount of carboxylic acid present at any time is extremely low.

The carboxylic acids do not have any activities of interest. Once the ester group is removed, it has done its job, and the parent drug acts in its normal manner.

Besides the simple chemical hydrolysis described above, the esters can be removed by enzymes in the blood called *esterases,* though water still is required for the reaction. The great majority of hydrolysis occurs with the help of these enzymes or by non-specific reactions with proteins. These reaction cannot take place while the esterified steroid is dissolved in fat. Thus, while the esterified steroids are dissolved in fat, they are protected from hydrolyis, and thus serve as a depot for the drug, giving extended duration of action.

What is the significance of the partition coefficient?

Differences in partition coefficient seem to account almost fully for the differences between various esters of anabolic steroids, as shown by Chaudry and James.[1,2] To understand their work, though, it is necessary first to consider the methods they used to obtain their data on the *anabolic* and *androgenic* effects of the drugs tested.

These scientists are not using those terms in the manner which many bodybuilding authors do. The anabolic effect is measured by increase in weight of the levator ani muscle in the rat, and the androgenic effect is measured by increase in weight of the seminal vesicles and prostate. These measurements are neither perfectly indicative of muscle-building value to bodybuilders nor to any particular undesired side effect except perhaps prostate enlargement. Despite the limitations of the method, this was the assay method available.

A number of esters of nandrolone were studied, using various single doses, but only the results from a single dose of 1 mg are given here. The results are as follows:

Parent Drug	**Ester**	**# of Carbons**	**Anabolic Effect**	**Anabolic / Androgenic Ratio**	**PRC** (P) x10^{-3}**
Nandrolone	formate	1	1176	13:1	15*
	acetate	2	1594	11:1	25*
	propionate	3	1880	10:1	41*
	butyrate	4	1488	7:1	69
	valerate	5	2526	9:1	115*
	hexanoate	6	3731	9:1	192
	heptanoate	7	6559	13:1	269
	octanoate	8	5557	15:1	611
	nonanoate	9	5080	19:1	455
	decanoate	10	7735	25:1	802
	undecanoate	11	6576	32:1	1460

*extrapolated from P of the butyrate ester
** partition ratio coefficient

The anabolic effect was found to be predictable according to the equation:

$$\log (\text{anabolic effect}) = 7.33 \log P - 0.636 \log P^2 - 17.8$$

The accuracy of predictions was quite high (r = 0.970) and the *F* value, indicating the statistical significance of the equation, was very high at 61. Thus, the observed anabolic effect of these ester prodrugs of nandrolone was found to be highly correlated with partition coefficient.

Higher partition coefficients were also strongly correlated with higher anabolic/androgenic ratio.

It was also found that the times of first and second peaks of drug level after injection were predictable from P with good accuracy and high significance.

How can the greatly higher anabolic effects of the long chain esters be explained?

While the authors do not make note of it in either article cited, there is a simple explanation for the observed result. Long chain esters of anabolic steroids are not many more times potent than short chain, if indeed they are any more potent at all. Yet in the above study, the undecanoate ester was found to give 3.5 times the effect of the propionate ester. Why?

There is a difference in pharmacokinetics (the time course of the drug in the body). Although the same 1 mg dose is being given in each case, it is either present in the serum of the animal at a relatively high concentration for a relatively short time for the shorter chain esters, or at lower concentration for a longer time for the longer chain esters. This difference can be quite large: the undecanoate ester can be predicted to have a half-life 36 times longer than that of the propionate ester.[3]

With most drugs, response is not proportional to the dose, but to the log of the dose. Assuming that the dose is well into the effective range, taking ¼ the dose does not result in only ¼ the result, but in ½ the result.

Viewed in this light, if the nandrolone propionate had been given in 36 divided doses over the same length of time that nandrolone undecanoate was in the system, in a manner to match its pharmacokinetics, one would expect 1/6 the result from each individual dose before accounting for molecular weight differences. The cumulative response would be 36 times 1/6, or six times the observed result from the single large dose. If we then correct for the lower molecular weight of the propionate ester, which delivers more nandrolone per mg. than does the undecanoate ester, we would predict 3.3 times more response than from the single large dose. In fact the observed response of the undecanoate ester was 3.5 times that of the propionate ester. This difference is within experimental error.

This calculation I have performed is also supported by experimental evidence performed by van der Vies[4]. His research showed that when the dose of nandrolone was divided into frequent small injections in such a pattern as to mimic the pharmacokinetics of esters, the anabolic effect became identical to that of the esters.

Thus, pharmacokinetics, the log dose/response curve, and differences in molecular weight are sufficient to account for observed differences in anabolic effect between different esters of an anabolic steroid, or between an ester and the parent drug.

This correlates with my observation that anabolic effect of testosterone esters is equal, so long as each is administered reasonably frequently: at least once per half-life, and preferably twice. E.g., if testosterone propionate yielding some given amount of testosterone per week is administered daily, or at least every other day, it will give results comparable to testosterone cypionate administered at least once every week, and preferably twice per week, that yields the same amount of testosterone per week.

How can the differences in anabolic/androgenic ratio be accounted for, and how significant are they?

Partition coefficient is key information for determining how a drug will be distributed in the body. The ratio of solubility between oil and water gives good relative predictions of the ratios of solubility between blood and target organs. Different target organs, for example the levator ani muscle vs. the prostate, may have different solubility properties. A more lipophilic drug (one with a high partition coefficient) would distribute much moreso into a more lipophilic target organ than into a less lipophilic one. It may then be the case that the longer chain esters partition more preferentially into muscle and less preferentially into the skin and prostate, but this is not demonstrated.

For this to be the case, it would be necessary for the esterified steroids to be distributed throughout the body after slow release from the oil depot injection site, rather than to have only free parent drug released from the injection site. This is an agreement with the findings of James *et al*.[3] which demonstrate that the esters do indeed become distributed throughout the body after injection.

I don't, however, expect that differences in distribution are the primary reason for observed differences in anabolic/androgenic ratio between different steroid esters. There is another possible explanation for differences in this ratio. In the same work referenced above concerning anabolic effect as a function of pharmacokinetics, van der Vies showed that if nandrolone is administrated with frequent dosage patterns designed to give the same trend of serum levels as seen with either phenylpropionate or decanoate, nandrolone itself gave the same anabolic/androgenic ratios as each of these esters of nandrolone.

What application does this information on anabolic/androgenic ratio have to female bodybuilding?

Since keeping androgen levels constant and moderate gives a higher anabolic/androgenic ratio than using the same total amount of drug per week but allowing levels to spike and then subside, female bodybuilders are better advised to use either long acting esters, or if short acting esters are used, to inject small doses frequently (twice per half-life). And for the same reason, a given amount of oral steroids per day is better taken in divided doses than in a single larger dose.

This is probably because tissues with sex-specific traits exhibit *thresholds* to effect of androgens. Below the threshold, nothing happens, but above it, cellular differentiation occurs. Thus, while female levels of androgens are about 10% that of a male's, 10 years of female levels of androgen will not grow as much beard or change the voice as much as one month of male levels. The threshold simply is not crossed at the lower levels, but is crossed at the higher levels.

Female bodybuilders will do better to avoid spikes in androgen level that cross this threshold. Therefore, consistent low doses are better than spiking with intermittent high doses, and advice to use 100 mg/week of testosterone propionate to avoid virilization simply makes no sense (and in practice, often fails.)

It should still be noted that some women will suffer virilization with almost any dose of anabolic steroid, regardless of dosing pattern.

What are the half-lives of different esters?

Shorter chain esters have shorter half-lives, because of their lower partition coefficient. Testosterone cypionate has a half-life of 8 days[5], the enanthate ester has a half-life of 4 days[6], and nandrolone decanoate has a half-life of 8 days[7]. These figures are only approximate. The difference between these values for cypionate and enanthate probably includes difference attributable to different measuring techniques. The actual difference is probably not more than two days.

In the rat, where half-lives of anabolic steroid esters are similar to those in humans but somewhat shorter, the half-lives of the phenylpropionate, decanoate, and laurate esters are 1, 5, and 10 days respectively.[3] The same trend would be expected in man.

Half-life is linearly related to log partition coefficient, which is itself linearly related to the carbon chain length, the exception being if the ester is an unusual one such as phenylpropionate. This was shown by James *et al.*[3] for the formate through valerate esters of testosterone in the rat. The half-life of testosterone propionate was approximately 4 days, and each carbon added to or subtracted from that chain length changed half-life by about 1.5 days.

How are steroid esters made, and can esters be made of prohormones?

The most convenient method of synthesis of steroid esters is reaction of the steroid in a 2:1 mixture of pyridine and the *anhydride* of the desired ester: for example, propionic anhydride would be used to make the propionate ester. A large excess (at least 10 times) of the anhydride compared to the steroid would be required. This would then be purified

by diluting with at least 10 parts of water to each part of pyridine, adding 1 part ether, decanting the water after shaking, and then washing with 10 parts water repeatedly in a separatory funnel. This would be followed preferably by recrystallization or chromatography for purification.

Esters cannot be made of dione prohormones because they do not have an –OH group. Esters can be made of the diols, but purification by recrystallization probably is not possible because the product would be a mixture of 3α and 3β esters, which could be expected to yield an oily mess, or perhaps an amorphous solid. Further difficulties would include the fact that for the diols, the starting material from at least some manufacturers is of considerably less than 100% purity. I personally would not even consider injecting the product of the above reaction without some further purification besides the water wash. An even more serious consideration is that by esterifying the prohormone, one is arguably manufacturing a controlled substance. To say the least, this is a real no-no with the Drug Enforcement Agency, even moreso than possession or importing, both of which are already quite serious crimes. Therefore I cannot recommend manufacturing esters of diol prohormones, but for the sake of completeness in an article on steroid esters, I thought I would mention how they can be made and what the difficulties are.

Can we make esters of Winstrol, Dianabol, etc., for injection?

While there are a number of interesting oral steroids that, at first glance, would be appealing candidates for making esters, in fact there are very good reasons why no such products are available. Indeed, there are absolutely no 17-alkylated steroid esters on the market.

First, they would be difficult to synthesize. The 17-methyl group which works to block liver enzymes from reacting with the steroid molecule will also hinder the material one would use to make the ester from reacting with the steroid.

More seriously, there is the fact that a 17-methyl would also block enzymes in the body from hydrolyzing (removing) the ester, which would be necessary to yield the active steroid.

So I do not expect that you will ever see esters of Winstrol, Dianabol, or any 17-alkylated steroid on the market, and don't recommend that anyone try making them. They would probably be inactive, or if they have any activity, it would be very low.

Summary, and Practical Implications

Shorter chain esters must be injected more frequently than longer chain esters if consistent blood levels are desired. Consistent blood levels probably lead to the greatest

efficiency of use for the drug and the highest anabolic/androgenic ratio. The activity of long chain esters can be mimicked by frequent administration of short chain esters.

While it has been alleged popularly that some esters aromatize more than others, there is no support for this in the scientific literature, and the concept makes relatively little sense since the ester itself is very far removed from the site of reaction of aromatization. The claims in this area seem flawed: for example, in World Anabolic Review 1996, the text makes plain that the comparison being made is between a weekly dose of 350 mg of testosterone propionate vs. a weekly dose of over a gram of testosterone enanthate or other long chain esters. While it is surely true that, as they say, side effects of the latter will be more pronounced than those of the former, it is unreasonable to attribute this difference to the ester used.

All testosterone drugs aromatize, and if estrogenic effects are not desired, then anti-estrogenic agents should be used for any of the esters and in the same manner, regardless of the ester used.

While the theory of the effects of esterification of steroids is interesting and somewhat complicated, the practical implications are simple. Differences between parent drugs are far more important than differences between esters of the same drug. And if the ester is different, the key difference to the bodybuilder is in half-life of the drug. Longer half-lives add convenience, and shorter-half lives allow the drug to exit the body more quickly. Short half-life also can allow fairly rapid drug clearance to occur before drug testing. Testosterone propionate is therefore a drug of choice for the tested athlete. And if a brief alternating cycle plan is being used, a short half-life allows high dosing during the "on" weeks with rapid clearance to non-inhibiting levels during the off weeks. Besides these things, however, there are no significant differences between drugs resulting from use of different esters.

Enzymatic Conversions and Anabolic-Androgenic Steroids

Anabolic/androgenic steroids (AAS), when introduced into the body, do not necessarily remain unchanged. Enzymatic processes often convert them to different molecules. This is true of the prohormones as well: androstenedione will not necessarily remain as androstenedione, but some of it will be converted to testosterone. Although that example is well known, many other enzymatic conversions of steroids are less well-known in bodybuilding. We will be looking at these conversions in this article.

Esterases

Anabolic steroids given by intramuscular injection are usually (not always) esterified versions of the parent drugs (Figure 1). This esterification improves the oil solubility of the steroid, and reduces water solubility: the result is that the esterified drug remains

stored mostly dissolved in fat, and the parent drug is released to the bloodstream only slowly, over time.

The enzymes that accomplish this transformation are called esterases, and are widely present in the body. Aside from allowing use of esterified drugs, they have another effect: they can also work in the reverse direction. Instead of removing an ester from the esterified drug, they can add an ester to the parent drug. This can increase the lifetime of the drug in the body. Thus, it could be expected that some small amount of a norandro prohormone would be converted to an esterified form, and would remain (in trace amounts) in the system for quite some time. Unfortunately, analytical techniques today are sufficient to detect nandrolone or its metabolites in extremely low concentrations. Thus, the norandro products cannot be recommended to anyone who might be subject to drug testing for AAS.

Esterases cannot work well on steroid esters that are 17alpha alkylated, because the alkylation blocks the approach of the enzyme to the ester. This is the reason that no such drugs are sold – there are no esters of Dianabol, methyltestosterone, Anadrol, oxandrolone, Winstrol, etc., and there never will be (Figure 2). They would be inactive.

3beta hydroxysteroid dehydrogenase (3bHSD)

This enzyme, like the esterase enzymes, can work in two directions. It can either convert a steroid that has a keto group on position 3 of the steroid (Figure 3, the left molecule) to one with a hydroxy group in the same position (Figure 3, the molecule on the right) or vice versa. The latter action is seen when androdiol is converted to testosterone by this enzyme. The former is seen when DHT is converted to androstanediol (not androstenediol) in muscle tissue (Figure 4): this is the reason DHT is not an effective anabolic in muscle tissue.) Proviron also undergoes this transformation and is deactivated in muscle tissue (Figure 5).

The conversion of DHT to androstanediol also occurs in scalp tissue, and androstanediol may be of relevance in the development of male pattern baldness.

Because the enzyme works in two directions, it cannot convert a keto steroid entirely to the hydroxy, or vice versa, because some of what is converted will then be acted upon again and return to its original state. Thus, there will always be a mixture of the two compounds. In some cases, the mixture might favor one side of the balance.

3bHSD is widely distributed in the body.

17beta-hydroxysteroid dehydrogenase (17bHSD)

Again, this is an enzyme that can work in two directions. It can convert a steroid that has a keto group in the 17 position (Figure 6, molecule on left) to one that has a hydroxy group in the same position (Figure 6, molecule on right), or vice versa. The former conversion takes place in the case of androstenedione being converted to testosterone.

Aromatase

This enzyme removes the 19 methyl from AAS and *aromatizes* the A ring (Figure 7). This means that three, alternating double bonds are formed in that ring. Any process which produces such a pattern of bonds is called aromatization, and the enzyme is called aromatase because it accomplishes this. It is worth noting that aromatization does not require aromatase in some cases: for example, in the case of nandrolone. However, in those AAS which have a 19 methyl, the aromatase enzyme is required for aromatization, since a double bond cannot be formed at carbon 10 unless the 19 methyl is removed. (A carbon atom can have only four bonds, and there would be five in such a case.)

Aromatase is the first enzyme we have discussed where we are interested in reducing its activity. This may be done by either of two types (usually) of inhibitors: *competitive* inhibitors and *mechanism-based (suicide)* inhibitors.

Competitive inhibitors act by binding to the same site of the enzyme as the steroid molecule would. Arimidex, for example, does this. Whatever percentage of enzyme has the inhibitor bound to it, is inactive for as long as the inhibitor is bound. Thus, a small amount of inhibitor might inhibit only a small percentage of the enzyme molecules, whereas a larger amount would inhibit a higher percentage.

The inhibitor also must compete with the steroid for access to the binding site. Thus, if there is a very high amount of steroid, the steroid will be likely to "get there first" and the inhibitor will be less effective: unless its concentration is likewise increased. Thus, while Arimidex may do an excellent job at 1 mg/day for an AIDS patient using 250 mg/week of testosterone, it may fail to outcompete 1 gram per week of testosterone unless the dose is increased. This problem is true of Cytadren also.

The other type of aromatase inhibitor is one that actually destroys the enzyme, and is itself destroyed in the process. These inhibitors are called mechanism-based (suicide) inhibitors. An example of this type is Lentaron. It has not seen much use in bodybuilding and its efficacy is not clear.

Aromatase is works in only one direction: it cannot convert an aromatized steroid back to an unaromatized one.

Aromatase cannot work on DHT, Proviron, Winstrol, oxandrolone, Halotestin, or Primobolan, and there is no evidence that it can work on trenbolone. It is not clear if it works on Anadrol or perhaps on an Anadrol metabolite. There appears to be no scientific evidence that Anadrol aromatizes to estrogen, a fact pointed out by Pat Arnold. It may be that it does not have estrogenic activity at all, but progestogenic activity. This also could be a potent inducer of gyno and bloating.

5alpha-reductase

This enzyme can do one thing and one thing only: convert a steroid with a double bond between carbon 4 and carbon 5 to one with a single bond between them (and also adding a hydrogen to each carbon so the total number of bonds remains correct.)

This means that it can convert testosterone to DHT (Figure 8) or nandrolone to DHN (Figure 9) but it cannot convert Winstrol or Anadrol (Figure 2) despite the uninformed claims of careless steroid authors. And although Dianabol does have a double bond between carbons 4 and 5, it nonetheless also is not converted by 5AR.

Both Type 1 and Type 2 versions (*isozymes*) of 5AR exist. Type 2 is present in the prostate, and Proscar is a good inhibitor of that isozyme. Type 1 is present in the scalp and skin, and unfortunately Proscar is a poor inhibitor for that type. There are a number of experimental Type 1 inhibitors, such as MK-386, which will likely be of use in treating acne or male-pattern baldness, but they are not on the market yet.

3-oxosteroid-4,5-isomerase

This enzyme is of no interest unless one is concerned with the conversion of DHEA or one of the 5-andro products to testosterone, where the enzyme is required to change the double bond from the 5 position to the 4 position of testosterone (Figure 10).

P450 enzymes (various)

A number of enzymes of the P450 class can *hydroxylate* steroids at various positions on the molecule by adding OH groups. This will deactivate the steroid, and the added hydroxy group also provides a position for further metabolism to make the steroids water soluble and more easily excreted. While some have suggested the idea of inhibiting P450 enzymes to get more "bang for the buck" from a given amount of steroid, the idea is a poor one, since there are many P450 enzymes that can act in this manner on steroids, and these enzymes are important for metabolism of many things other than steroids. Where there might be some relevance is if a drug is taken which greatly increases amount of some P450 enzymes; for example, rifampin. This would probably reduce the effectiveness of steroids by speeding their rate of metabolism.

UDP-glucuronysyltransferase (UDPGT)

This enzyme attaches what is basically a sugar molecule to an –OH group of a steroid, thus deactivating it and making it far more water soluble, and more readily excreted.

This action is reversible to a minor extent in the body by glycosidase enzymes. It is reversed to a significant extent, however, in what is called *enterohepatic recycling.* In this process, deactivated, glucuronidated steroids are excreted in the bile into the intestine, where bacteria then cleave the glucuronide, restoring the steroid. Much of this steroid will then be reabsorbed by the body. The result is, just because a steroid is excreted once, doesn’t mean it still won’t come back for another turn. This phenomenon is quite important in birth control, and is the reason why antibiotics can interfere with The Pill.

The amount of bacteria in the intestine is reduced by the antibiotics, which reduces the degree of recycling, and thus reduces estrogen levels. It would also be the case, for an androgen user, that antibiotic use would reduce enterohepatic recycling, and thus cause a given dose of steroid to have less effect.

Men have about twice as much UDPGT activity on steroids as women do. There is also a great deal of variation between individuals.

Sulfotransferases (various types, including DHEA-ST)

These enzymes convert a –OH group of a steroid to the sulfate form, which is inactive. The process is reversible. The sulfated form provides a depot of temporarily inactivated steroid which may be later converted back to the parent steroid. This is of particular relevance with DHEA, where a large fraction of DHEA is in the sulfated form at any given moment, but is also of some relevance with the diol prohormones, which may be sulfated, and therefore inactivated, at the 3-OH position.

Sulfation generally occurs at a slower rate than glucuronidation, but nonetheless the process is still significant in the metabolism of testosterone, where conversion in the liver to the sulfate inactivates the drug and makes it more readily excreted in the bile (and again, enterohepatic recycling can occur.)

Summary

Enzymes are necessary to activate esterified steroids (the drug is inactive as long as the ester group remains present) and are necessary to deactivate steroids or to make them more water soluble and more readily excreted. They are also necessary to convert the prohormones to the active hormones. Aromatase and 5AR both convert testosterone to active compounds which may have different activities: to estrogen (in the case of aromatase) or to DHT, a more potent androgen, in the case of 5AR. 3bHSD also can convert an active compound, DHT, to androstanediol (not androstenediol) which while it is not active at the androgen receptor, may be of relevance in the development of male pattern baldness.

Control of the aromatase enzyme by inhibitors is recommended if aromatizable steroids with a C19 group (e.g., testosterone, Dianabol) are being used. A 5AR inhibitor is recommended in cases where testosterone is being used and the individual is particularly concerned about the prostate. Should a Type 1 5AR inhibitor become available, it would be of use in limiting the acne-inducing and male pattern baldness accelerating activities of testosterone.

Addendum: reading the chemical figures (this can be omitted if you are not concerned with chemistry):

Where lines meet, or a line ends with no letter at that end, there is a carbon atom. Each carbon atom will have four bonds. Lines that are drawn are bonds. In some cases, a double line may be used: this indicates a double bond that counts as two bonds. If the number of bonds is not four, then there are also hydrogen atoms present sufficient to give enough bonds. For example, \/\/\ would be a shorthand representation of:

```
   H H H H H H
   | | | | | |
H-C-C-C-C-C-C-H
   | | | | | |
   H H H H H H
```

Clearly, the shorthand line form is more convenient to write, and easier for the eye to read. The steroid framework is easy to see with the line structure, but would be very cluttered if all the carbons and hydrogens were explicitly drawn.

C represents a carbon atom, H represents a hydrogen atom, O represents an oxygen atom, and N represents a nitrogen atom.

An Integrated Drug, Training, and Nutrition Program

There has been considerable interest from readers in the brief alternating cycle concept that I have previously discussed. Here, I give an example of an actual program that has been used successfully. The athlete who followed this particular program has completed four such six-week cycles (only two of each six weeks featured substantial steroid use), with a net muscle gain of 25 lb and a net fat loss of 5 lb. The last three of those cycles gave a net muscle gain of 14 lb and a net fat loss of 14 lb. This has been for a consecutive 24 weeks, yet there has been no loss in testicle size, despite the fact that HCG was never used, nor loss of normal functioning by any measure during off weeks (with a single exception.) Thus it seems that LH production remained sufficient to maintain normal testosterone production through four consecutive cycles.

This program has not been exactly as described for all four cycles, but has been modified slightly as time has gone on. This is the most current version. The athlete believes that this version could have been followed from the beginning with equally good or superior results. Differences really are not significant.

This information is not provided as a recommendation for anyone to follow, but for informational purposes of what some current thinking is in this area. We do not advocate illegal use of drugs, but note that many individuals successful in bodybuilding engage in such use, and consider that dissemination of such information is in the interest of an informed public.

Manner of exercise performance

All sets of an exercise are generally performed with the same weight. Rest between sets is usually four minutes, which may be extended to five minutes for deadlifts and squats (four minutes if 10 sets are being performed.) Calves usually receive 2 minutes rest. Tempo is usually 4 second negatives with powerful, somewhat explosive positives. However, on phase 5, negatives are only 2 seconds. On rowing and pulldown exercises, full contraction is held for one second. During phases three and four, on the last set of an exercise, generally the final negative is extremely slow, and if the fully lowered position gives a good stretch, the stretch is held for 15 to 20 seconds after that last rep. On all other phases the final negative is normal.

Squats are only about 2 seconds on the negative. There is nothing wrong with 4 second negatives on squats, but this athlete cannot stand them psychologically. Squats are below parallel, and are performed with a Manta Ray.

Generally, multiple sets are for the same number of reps, but not necessarily. E.g., when performing 2 sets, the first set would end probably 1 rep short of maximal, but the second set would be maximal and probably that same number of reps. Often when three sets are performed, the final set will be fewer reps than the first two. However, sets of five are generally performed with the same number of reps for each set, using previous experience as a guide.

"Failure" – attempting and straining to lift a weight that can no longer be lifted – is avoided like the plague. There is no evidence that failure itself stimulates growth at all, and it certainly appears to be likely to result in nervous overtraining, even with far fewer sets performed per week than in this program.

Instead, once a rep is so difficult to complete that the lifter, from experience, knows that it cannot be lifted again, the set is to be completed with a final negative (in exercises allowing that.) There is no attempt to lift the weight when it can no longer be lifted. That should only occur in rare cases of mis-estimation of one's ability to do another rep.

Overall training scheme

The cycle is composed of five phases, which are quite similar to each other but which vary in the weight used. The first three phases are 8 days each, and the second two phases are 10 days each. Therefore, all five phases take 44 days, or just over 6 weeks.

Weight increases between phases are approximately equally divided: e.g., phase 4 might be 20 lb heavier than phase 3, which in turn would be 20 lb heavier than Phase 2, which in turn would be 20 lb heavier than Phase 1. Phase 5 generally has no weight increase from Phase 4, unless more reps were performed than expected in Phase 4.

Phases 1 and 2 are performed under natural conditions or with light drug use, with light weights which lead into the heavier weights used in weeks 3 and 4. Reps will be fairly high in these weeks: about 9-14 reps for upper body exercises, and as much as 20 reps for

squats. Some exercises that will be performed in Phases 3 and 4 are omitted, and often fewer sets are performed.

Phases 3 and 4 are performed using the full amount of drugs listed. The weights are heavier, and reps will fall to as low as about five or six.

Phase 5 is performed with the same weights as Phase 4, or slightly heavier if reps were more than six in Phase 4. However, negatives are faster, at 2 seconds per rep, and sets will be fewer. Light drug use during this phase gave better results than use of no anabolics.

Weights given are as percentages of maximums achieved on Phase 4 of the previous cycle, or previous personal record. Generally the number is not that achieved for a single set, but for two consecutive sets. Thus, "80% 5RM" would mean, 80% of that weight for which one had previously obtained 5 reps on the second set of that exercise.

Usually, in periodization plans, percent 1RM is used as the guideline, but this athlete did not have 1RM values for most lifts. Thus, values such as 5RM and 6RM were used. The general concept was for Phases 1 and 2 to be at about 60% and 68% 1RM, for Phase 3 to be at about 76% 1RM, and for Phase 4 to be at about 84% of the previous 1RM. However, 1RM values may have been misestimated, and are not given here, though these estimates were used in planning the cycle.

For Hammer Strength machines, only the weight of the plates is counted. This does result in some inaccuracy. However the athlete has not measured the tare weight of these machines and therefore this is not accounted for.

For squats, 75% of bodyweight is assumed to be lifted along with the barbell, as recommended by Poliquin. Thus, if 5 RM is 300 lb and the lifter weights 200 lb, in calculations this would be figured as 450 lb. 67% of that (for example) would be 300 lb. That would require a 150 lb barbell in this example, since 150 lb of bodyweight is also being lifted, making a total of 300 lb. This formula is probably accurate for the legs but is inaccurate for the lower back: loads will be a smaller percentage than expected. However, training the lower back is not the purpose of squatting.

Drug selection

Trenbolone acetate (50 mg/day) and Dianabol (10 mg five times per day) were the chosen anabolics for all cycles, except that the last cycle also included 50 mg/day Winstrol Depot. This addition resulted in gains equal to previous cycles despite considerably reduced calorie intake compared to previous cycles. Clomid was used, generally at 100 mg/day when using 50 mg/day total of Dianabol, and 50 mg/day otherwise. Cytadren was used, 250 mg/day (125 mg on arising, and 62.5 mg six and twelve hours later), when Dianabol was used at 50 mg/day total, and only 125 mg/day, on arising, when only 20 mg.day Dianabol was being used. Primobolan Depot, 400 mg, was used at the start of week 5 in those cycles when orals were used in weeks 5 and 6. No other drugs were used.

Drug schedule

Weeks 1 and 2: Clean, but using 50 mg/day Clomid if there was a preceding cycle. Optionally, a low dose of an oral anabolic might be used in the morning: 10 mg Dianabol on arising, and 10 mg four hours later. If this is used, then 125 mg of Cytadren is taken upon arising. 300 mg Androdiol is taken before workouts, but not after 4 PM. (I do not have proof that inhibition of LH production would occur if the Androdiol were taken later, but suspect that that might be the case.)

Weeks 3 and 4: Trenbolone acetate and Dianabol at 50 mg/day, optionally with Winstrol Depot at 50 mg/day. Cytadren at 250 mg/day, and Clomid at 100 mg/day. It is not certain that this much is required: 50 mg might suffice. A double dose of trenbolone acetate was used on the first day of week 3, and none was used on the last day of week 4.

Week 5 and 6: Light use, as described as being optional for weeks 1 and 2, but preceded with 400 mg Primobolan Depot at the start of week 5. For two of the four cycles, there was no such use. In one case (the first cycle), there were no losses, but in the second case (the third cycle) there were. In the second and fourth cycles, light use in weeks 5 and 6 resulted in no losses, and in fact gains in week 5. Therefore it is thought better, at least for this particular lifter, to have the support of the low dose usage during the "off" weeks, or at least during the first two weeks following the two heavy weeks.

Nutrition program

The basic scheme was that for weeks 1 and 2, calories were at 12 calories per lb of lean body mass, using a cyclic ketogenic diet or an isocaloric diet. One gram protein per lb LBM was used. Weeks 3 and 4 usually featured heavy eating, with at least 55 g protein per meal and at least seven meals or protein shakes per day, usually with attendant fat gain. However, for the fourth cycle when Winstrol was used, while protein levels remained high, fat intake was kept very low, so total calories were moderate, and there was no net fat gain. Weeks 5 and 6 are isocaloric at maintenance calories, with about 55 g of protein each meal for week 5, and 35-40 g for week 6.

The only supplements used were Met-Rx, Met-Rx Protein Plus, Substrate Solutions Androdiol, ephedrine, caffeine, and a mixture of flax, borage, and hemp oils. Ephedrine and caffeine were used prior to workouts in all cases, and three times per day during weeks 1 and 2 (the dieting weeks.) In the future, DHEA supplementation at 50 mg/day, might be added, not for anabolic effect, but to compensate for low DHEA levels resulting from steroid use.

The complete program, day by day

The five entries after each exercise refer to Phases 1, 2, 3, 4, and 5, respectively. The RM used is the same for each entry, but the reference to the number of reps is given only for the first entry.

Day 1

Phase	1	2	3	4	5
Seated Military Press (on a bench):	2 sets, 68% 6RM	2 sets, 80%	3 sets, 92%	3 sets, 104%	2 sets, 104%
Seated DB Overhead Press (on a bench):	Omit.	Omit.	3 sets, 100% 5RM.	3 sets, 108%.	2 sets, 108%
Smith Military Press, seat leaning back a little:	2 sets, 67% 5RM.	2 sets, 80%.	3 sets, 93%.	3 sets, 107%.	2 sets, 107%.
Hammer Calf:	2 sets, 67% 7RM.	2 sets, 80%.	3 sets, 93%.	3 sets, 107%.	2 sets, 107%.
(Rest three hours.)					
Bench Press:	2 sets, 71% 4RM.	2 sets, 82%.	5 sets not to exceed 10 reps, 66% with one minute rest, then 5 more with 4 minutes rest.	Same, but with 70%.	5 sets of 5,4,3,2,1 reps respectively, with 92% to 113%, then one set with 102%.
Incline DB Front Raise:	Omit.	Omit.	3 sets, 100% 8RM.	3 sets, 120%.	3 sets, 120%.
Hammer Calf:	Omit.	Omit.	10 sets of 10 with 76% 7RM, one minute rest.	10 sets of 10 with 80%, one minute rest.	2 sets with 100%, two minutes rest.

Hammer Incline Bench:	2 sets, 75% 5RM.	2 sets, 84%.	2 sets, 94%.	2 sets, 103%.	2 sets, 103%.

Day 2

Phase	**1**	**2**	**3**	**4**	**5**
Hammer High Row (performed as one-and-a-quarter reps, with the additional ¼ being a repeat of the last, contracted part of the rep):	2 sets, 65% 4RM.	2 sets, 78%.	2 sets, 91%.	2 sets, 105%.	2 sets, 105%.
Hammer Low Row:	2 sets, 69% 5RM.	2 sets, 81%.	2 sets, 95%.	2 sets, 107%.	2 sets, 107%.
Hammer Iso Row, one arm at a time:	2 sets, 66% 5RM.	2 sets, 79%.	2 sets, 91%.	2 sets, 106%.	2 sets, 106%.
Med-X Pullover:	2 sets, 66% 5RM.	2 sets, 79%.	2 sets, 93%.	2 sets, 106%.	2 sets, 106%.
Wide Grip Pullups followed immediately by Medium Grip Chins:	Omit.	Omit.	Three sets.	Three sets.	Two sets.
(Rest three hours)					
Med-X Lying Leg Curl:	2 sets, 67% 7RM.	2 sets, 81%.	2 sets, 95%.	2 sets, 108%.	2 sets, 108%.
Med-X Leg Extension:	2 sets, 66% 8RM.	2 sets, 78%.	2 sets, 92%.	2 sets, 105%.	2 sets, 105%.
Med-X Seated Leg Curl:	2 sets, 78% 8RM.	2 sets, 93%.	2 sets, 108%.	2 sets, 123%.	2 sets, 123%

Med-X Leg Extension:	Omit.	Omit.	2 sets, 92%.	2 sets, 105%.	Omit.
Deadlift:	1 set, 78% (5 sets of 5)RM.	2 sets, 88%.	5 sets, 100%.	5 sets, 107%.	Five sets of 5,4,3,2,1 respectively at 110% to 125%, then one set with 103%.
Seated Good Morning:	1 set, 74% 9RM.	2 sets, 87%.	2 sets optional, 100%.	2 sets optional, 112%.	2 sets optional, 112%.
Med-X Abdominal:	Omit.	1 set, 104% 10RM.	Two sets, 106%.	Two sets, 108%.	Two sets, 108%.

Days 3 and 4:
rest. Note – phases 1 and 2 receive an extra day rest.

Day 5 (or 6, for phases 1 and 2)

Phase	**1**	**2**	**3**	**4**	**5**
Bench Press:	2 sets, 76% 4RM.	2 sets, 87%.	3-5 sets, 95%.	3-5 sets, 105%.	2 sets, 105%.
Hammer Lying Bench Press:	2 sets, 63% 5RM.	2 sets, 76%.	3 sets, 89%.	3 sets, 105%.	2 sets, 105%.
Seated DB Overhead Press (on a bench, hands off center, with outer edges of hands against outside plates):	2 sets, 75% 5RM.	2 sets, 83%.	3 sets, 92%.	3 sets, 100%.	2 sets, 108%
Hammer Calf:	Omit.	Omit.	3 sets, 100% 7RM.	3 sets, 113% 7RM.	2 sets, 113% 7RM.
Hang Cleans, 8 reps:	1 set, 74% 8RM.	2 sets, 85%.	3 sets, 96%.	3 sets, 107%.	2 sets, 107%.
Hammer Seated Calf:	Omit.	Omit.	2 sets, 100% 14RM.	2 sets, 104%.	Omit.
(Rest 3 hours)					

Seated Military Press:	2 sets, 72% 6RM.	2 sets, 84%.	3 sets, 96%.	3 sets, 108%.	2 sets, 108%.
Hammer Calf:	2 sets, 73% 7RM.	2 sets, 87%.	3 sets, 100%.	3 sets, 113%.	2 sets, 113%.
Smith Shrugs:	2 sets, 67% 5RM.	2 sets, 81%.	3 sets, 94%.	3 sets, 107%.	2 sets, 107%.
Hammer Row:	2 sets, 66% 6RM.	2 sets, 80%.	2 sets, 95%.	2 sets, 109%.	2 sets, 109%.
Hammer Behind Neck Pulldown, one arm at a time:	1 set, 66% 5RM.	2 sets, 81%.	2 sets, 95%.	2 sets, 110%.	2 sets, 110%.
Bent Row, Yates-style (bent over only 20 to 30 degrees, pulling to just above waistband of shorts, keeping shoulders down not shrugged) :	1 set, 64% 6RM.	2 sets, 78%. .	3 sets, 91%.	3 sets, 104%.	2 sets, 104%

Day 6 (or 7, for phases 1 and 2)

Phase	**1**	**2**	**3**	**4**	**5**
Med-X Lying Leg Curl:	2 sets, 74% 7RM.	2 sets, 92%.	2 sets, 102%.	2 sets, 108%.	2 sets, 108%
Med-X Leg Extension:	2 sets, 72% 8RM.	2 sets, 84%.	2 sets, 97%.	2 sets, 106%.	2 sets, 106%.
Med-X Seated Leg Curl:	2 sets, 85% 8RM.	2 sets, 100%.	2 sets, 115%.	2 sets, 129%.	2 sets, 129%.
Med-X Leg Extension:	Omit.	Omit.	2 sets, 97%.	2 sets, 106%.	Omit.
Squat:	1 set, 85% (5 sets of 5)RM.	2 sets, 92%.	5 sets of five at 100% followed by	5 sets of 10 at 77%. Same, but 106% and	5 sets at 106%.

				83%.	
Med-X Ab:	1 set, 102% 10RM.	2 sets, 104%.	2 sets, 106%.	2 sets, 108%.	2 sets, 110%.

Days 7 and 8: rest.
(Note – phases 1 and 2 receive an extra day rest.)

Repeating the cycles

The next cycle would follow with weights approximately 5-8% heavier on average than the one just completed, but adjusted if the rep range appears to need modification.

While an 5-8% gain every 6 weeks might not seem like much to a beginning lifter, for a more advanced lifter, putting together several such cycles results in gains that are quite impressive. This is the secret to periodization – the body constantly experiences different challenges, e.g. %RM – and over time the increases in weight are significant but achievable. In contrast, for an advanced lifter, attempting to do similar workouts every week but with say 1% more weight each workout soon results in stagnation and loss of a rep (or loss of lifting form) as a result of the weight increase, and no long-term increase in strength. Neither is it possible for an advanced lifter who already is lifting with maximal effort for a given weight to achieve an additional rep each week.

Most powerlifting titles have been won by individuals following planned training cycles, which, in the core lifts, follow a pattern which repeats from cycle to cycle, but slightly heavier each time. Aside from its success with the particular athlete who followed the program described here, this general approach has been successful for many strength trainers.

It appears, however, to be somewhat novel to have a drug program which integrates with the training program in such a way as to allow full recovery of natural testosterone production over more than half of each cycle, thus allowing the cycles to be repeated back to back many times without loss of normal testosterone production.