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W I L L I A M L L E W E L L Y N ' S

# ANABOLICS

10th Edition

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## **Preface**

ANABOLICS is a reference manual of drug compounds used to enhance body composition, strength, and/or athletic performance. This book includes an extensive review of the history, global availability, and application of anabolic/androgenic steroids, as well as related performance-enhancing drugs such as human growth hormone, insulin, anti-estrogens, diuretics, reductase inhibitors, and fat loss agents. The core focus of ANABOLICS is to provide a nonbiased and comprehensive review of the current science surrounding these drugs, as well as their medical and non-medical use. The effort of this book is always to help readers understand the potential risks of these drugs, in addition to their benefits. ANABOLICS is not intended to promote steroid or other drug use, but is designed to help readers, may they be physicians, patients, or illicit users, better understand these drugs, and make well-informed decisions about them.

Regular readers will notice the latest edition includes updates and new additions in the following sections:

### **Anabolic Overview (Part I):**

Part I was extensively updated in the 9th Edition of ANABOLICS, though the 10th Edition has seen some minor edits, and the addition of a section on AAS-linked tendon injury.

### **Practical Application (Part II):**

A new chapter of Counterfeit Steroid Detection has been added. It discloses techniques for identifying deviant products with a handheld microscope.

The Harm Reduction section has been modified, along with a follow-up chapter on Sterilizing Injectable AAS preparations.

The Post-Cycle Therapy section has been updated to include a modified PCT program, and Start of PCT timing calculations.

An Off-Cycle Therapy (OCT) section has been added, which discusses ways to better retain muscle mass between cycles, and make follow up programs more productive.

A chapter on Obtaining AAS has been added, which covers the popular ways these medications are obtained. This section includes advice about reducing risks.

### **Drug Profiles (Part III):**

Updates concerning drug manufacture and global availability have been made in most of the common Anabolic/Androgenic Steroid Profiles.

New or extensively re-written profiles have been added for Catapres (clonidine), Geref (sermorelin), Glucophage (metformin), and BP Stabil.

### **Steroid Availability Tables (Appendix A):**

Global steroid manufacturing status has been extensively updated. Many dozens of new steroid preparations have been added, and numerous out of commerce steroids have been removed.

### **Photographic Database (Appendix B):**

The photographic database has been extensively expanded, and includes approximately 3,000 pictures of anabolic/androgenic steroids and other drugs. Legitimate pharmaceuticals are labeled and grouped by their country of manufacture. The following terms are used to identify the origin of individual drug products.

**Real (or no specification other than country):** These legitimate pharmaceutical products are distributed in pharmacies or veterinary clinics in the labeled country of origin. Real drugs offer the greatest assurance of product purity and safety, although production standards may vary by country or market (veterinary/human).

**Counterfeit (CF):** This is an illicit duplicate of a real drug product and/or manufacturer. These items are of unknown quality and safety, and often contain substitute or no steroid ingredients.

**Export (EX):** These are drugs made by registered pharmaceutical companies, but are not licensed for sale in their

country of origin. They must be exported. Export products should be made in legitimate pharmaceutical manufacturing facilities, but depending on the region may not be made under the same close government supervision as locally distributed products.

**Underground (UG):** These products are made from unlicensed illegal manufacturers specifically for sale on the black market. Due to the completely unregulated nature of these drugs, they offer little assurance of quality, and are generally not recommended.

**Fake:** This is an illicitly manufactured drug that purports to be a real pharmaceutical, but bears no relation to an actual product. Fake is a distinction that suggests all forms of the photographed steroid should be considered illegitimate.

**NLM:** Indicates a drug that is No Longer Manufactured. This distinction is important because when NLM drugs are still found in active black market commerce they usually turn out to be illegitimate.

**New Service (HRT-Rx):**

As longtime advocates of the legitimate medical use of anabolic/androgenic steroids, we have launched HRT-Rx, a national referral service to help patients find progressive HRT/Anti-Aging physicians. Network doctors are the type that regularly work with testosterone medications, and understand the value of hormone replacement and optimization therapies. You can find a physician near you at [www.HRT-Rx.com](http://www.HRT-Rx.com). Note that most offices require you are at least 30 years of age to make an appointment.



**New Service (HRT-Labs):**

We have also partnered with a laboratory that can run extensive blood tests including hormone levels, liver/kidney enzymes, and general health markers. The service is available in all 50 states and can be accessed at [www.HRT-Labs.com](http://www.HRT-Labs.com).

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## Clinical Applications

Anabolic/androgenic steroids are approved for sale by prescription in virtually every pharmaceutical market around the world. Having been applied for many decades to treat a variety of diseased states, today these drugs have a number of well-established medical uses. They have been used to treat most patient populations, including men and women of almost all ages, ranging from children to the elderly. In many instances anabolic/androgenic steroids have proven to be life saving medications, which is a fact easily overlooked with all of the discussion about steroid abuse. This section details some of the most common and accepted medical applications for anabolic/androgenic steroids.

### Androgen Replacement Therapy/Hypogonadism

The most widely used medical application for anabolic/androgenic steroids in the world is that of androgen replacement therapy. Also referred to as Hormone Replacement Therapy (HRT) or Testosterone Replacement Therapy (TRT), this therapy involves the supplementation of the primary male hormone testosterone to alleviate symptoms of low hormone levels (clinically referred to as hypogonadism). Patients may be adolescent males suffering from childhood hypogonadism or a specific disorder that causes androgenic hormone disruption, although most of the treated population consists of adult men over the age of 30. In most cases hormone levels have declined in these men as a result of the normal aging process.

The most common complaints associated with low testosterone in adult men include reduced libido, erectile dysfunction, loss of energy, decreased strength and/or endurance, reduced ability to play sports, mood fluctuations, reduced height (bone loss), reduced work performance, memory loss, and muscle loss.<sup>50</sup> When associated with aging, these symptoms are collectively placed under the label of "andropause". In a clinical setting this disorder is referred to as late-onset hypogonadism. Blood testosterone levels below 350ng/dL are usually regarded as clinically significant, although some physicians will use a level as low as 200ng/dL as the threshold for normal. Hypogonadism is, unfortunately, still widely under-diagnosed. Most physicians will also not recommend treatment for low testosterone unless a patient is complaining about symptoms (symptomatic androgen deficiency).

Androgen replacement therapy effectively alleviates most

symptoms of low testosterone levels. To begin with, raising testosterone levels above 350ng/dL (the very low end of the normal range) will often restore normal sexual function and libido in men with dysfunctions related to hormone insufficiency. With regard to bone mineral density, hormone replacement therapy is also documented to have a significant positive effect. For example, studies administering 250 mg of testosterone enanthate every 21 days showed a 5% increase in bone mineral density after six months.<sup>51</sup> Over time this may prevent some loss of height and bone strength with aging, and may also reduce the risk of fracture. Hormone replacement therapy also increases red blood cell concentrations (oxygen carrying capacity), improving energy and sense of well-being. Therapy also supports the retention of lean body mass, and improves muscle strength and endurance.

Unlike steroid abuse, hormone replacement therapy may have benefits with regard to cardiovascular disease risk. For example, studies tend to show hormone replacement as having a positive effect on serum lipids. This includes a reduction in LDL and total cholesterol levels, combined with no significant change in HDL (good) cholesterol levels.<sup>52 53</sup> Testosterone supplementation also reduces midsection obesity, and improves insulin sensitivity and glycemic control.<sup>54</sup> These are important factors in metabolic syndrome, which may also be involved in the progression of atherosclerosis. Additionally, testosterone replacement therapy has been shown to improve the profile of inflammatory markers TNF-, IL-1,, and IL-10.<sup>55</sup> The reduced inflammation may help protect arterial walls from degeneration by plaque and scar tissue. The medical consensus today appears to be that replacement therapy in otherwise healthy men generally does not have a negative effect on cardiovascular disease risk, and may actually decrease certain risk factors for the disease in some patients.

There are some concerns with initiating testosterone replacement therapy when the individual is in poor health. One study examined the safety of HRT in men aged 65 and older with limited mobility and various health conditions such as obesity, hypertension, diabetes, or hyperlipidemia.<sup>56</sup> Each subject took a transdermal testosterone gel (10g/100mg) or placebo gel daily for six months. During the course of treatment, a total of 23 men in the testosterone group had cardiovascular-related adverse events. This was compared to only 9 in the placebo group. Another study with middle-aged

hypogonadal men found that testosterone replacement therapy (testosterone enanthate 250mg/2 weeks) reduced vascular reactivity, an important factor in atherosclerosis.<sup>57</sup> These studies suggest that care should be taken when considering HRT in men with heart disease, strong contributing factors to heart disease, or other chronic health conditions.

There are other areas of concern with elderly patients. To begin with, testosterone administration may increase prostate volume and PSA values.<sup>58 59</sup> While this does not appear to be of clinical significance with normal healthy patients, benign prostate hypertrophy and prostate cancer can be stimulated by testosterone. Men with prostate cancer, high PSA values, or breast cancer are generally not prescribed testosterone. Androgen supplementation has also been linked to sleep apnea, which can interfere with the most restful (REM) phase of sleep.<sup>60</sup> The studies have produced conflicting data, however, and the potential relationship remains the subject of much debate.<sup>61</sup> Lastly, testosterone replacement therapy has demonstrated negative, positive, and neutral effects on cognitive functioning in elderly men.<sup>62 63 64</sup> Studies do suggest that the dose can dictate the level of response, with the most positive effects noted when the androgen level reaches the mid-to upper-range of normal, not supraphysiological.<sup>65</sup> Elderly patients with preexisting deficits in cognitive function should have their cognitive performance and blood hormone levels monitored closely during hormone replacement therapy.

*Common Treatment Protocols:*

**Transdermal:** Transdermal application is the most commonly prescribed method for supplementing testosterone in the United States and Canada, and is generally the first course of therapy initiated with androgen replacement therapy patients. This method of drug delivery offers a number of advantages to the patient when compared to injection. Since the transdermal application is painless, patient compliance and comfort is increased in comparison. Transdermal application also provides stable day-to-day hormone levels, and does not produce the broad fluctuations usually noticed with injectable testosterone esters. The most common protocol among hormone replacement doctors is to prescribe a dosage of 2.5-10 mg of testosterone per day (approximate absorbed dose). This is applied as a rub-on gel or adhesive transdermal patch that is replaced daily. Note that due to metabolism in the skin, transdermal application of testosterone tends to increase serum dihydrotestosterone (DHT) levels more profoundly than testosterone injection. This may exacerbate androgenic side effects during therapy in

some patients, causing some to seek out injectable forms of testosterone as an alternative.

**Injection:** Testosterone enanthate and testosterone cypionate are the most widely prescribed injectable testosterone drugs in the United States and Canada. In many other markets the blended ester products Sustanon 100 and Sustanon 250 are also commonly prescribed. Injection of one of these testosterone ester products will provide the patient supplemental androgen levels for approximately 2 to 3 weeks after each application. The most common protocol among hormone replacement doctors is to administer 200 mg of testosterone enanthate or cypionate once every 2 to 3 weeks. It is important to remember that testosterone esters will deliver varying levels of testosterone to the body on a day-to-day basis throughout each application window. Levels will be highest the first several days after injection, and will slowly decline to baseline over the following weeks. Physicians are usually encouraged to monitor their patients closely to ensure androgen supplementation is sustaining hormone levels within the normal range (and alleviating symptoms of hypogonadism) throughout the entire therapeutic period. The longer acting injectable testosterone preparation Nebido (testosterone undecanoate) is undergoing review in the U.S., and has already been approved in other markets. This drug requires only 4 to 5 injections per year for most patients.

**Oral:** Testosterone undecanoate (Andriol) is the only prescription medication that delivers testosterone via an oral capsule. This medication is not approved for sale in the United States, but is a prescription drug in Canada and many other markets around the world. Patient compliance and comfort are high with this form of therapy, as there are no special routines or requirements aside from taking a few capsules each day with meals. Oral testosterone undecanoate is usually given at an initial dosage of 120 to 160 mg per day, which equates to three to four 40 mg capsules. This dosage may be reduced in subsequent weeks to 120 mg per day. The capsules are given in two divided doses per day, which are usually taken with breakfast and dinner. While this form of therapy is highly convenient, serum hormone levels can fluctuate greatly on a day-to-day basis. The amount of fat consumption has a particularly strong impact on hormone bioavailability, and meals providing at least 20 grams of fat are recommended when taking the capsules for maximum absorption. Note that as with transdermal testosterone, oral testosterone undecanoate tends to increase serum dihydrotestosterone (DHT) levels more profoundly than testosterone injections.

### Angioedema, Hereditary

Anabolic steroids are commonly prescribed for the treatment of hereditary angioedema, a rare and potentially life-threatening disorder of the immune system. Hereditary angioedema is caused by genetic mutations of blood clotting factors, characterized by a decrease in the level or functioning of the protein C1 esterase inhibitor. This protein controls C1, which is a "complement system" protein that plays an important role in the control of inflammation. Symptoms of hereditary angioedema include an intermittent but rapid swelling of the hands, arms, legs, lips, eyes, tongue, or throat. Swelling may also be noticed in the digestive tract, resulting in abdominal cramping, nausea, or vomiting. In the most serious cases, the patient may notice a swelling of the throat and a blockage of the airway passages, resulting in asphyxiation and sudden death. Many attacks occur without a specific trigger, although stress, trauma, surgery, and dental work are commonly associated with angioedema attacks.

Oral c-17 alpha alkylated anabolic/androgenic steroids have been shown to be a useful form of preventive therapy, stabilizing complement system protein levels and reducing the frequency and severity of angioedema attacks.<sup>66</sup> They are usually administered in a low dose, which is to be taken for long-term support of this disorder. The anabolic steroids that have been most commonly used in the United States for this purpose are stanozolol and danocrine, although historically many other agents have also been prescribed including oxandrolone, methyltestosterone, oxymetholone, fluoxymesterone, and methandrostenolone. The amount of steroid needed can vary depending on the individual, and is usually maintained at the lowest therapeutically effective dosage in an effort to offset undesirable side effects. FDA approved prescribing guidelines for stanozolol recommended an initial dosage of 2 mg three times daily (6 mg per day). This would be slowly adjusted downward to a maintenance level after a positive response was noted, usually to 2 mg given once every 1 to 2 days.

### Anemia

As a class of drugs, anabolic/androgenic steroids stimulate the synthesis of erythropoietin in the kidneys, a hormone that supports the manufacture of new red blood cells. By doing this, the administration of steroids tends to increase the red cell count and hematocrit level, making them of tangible therapeutic value for treating certain forms of anemia (a disease characterized by insufficient red blood cell production). Forms of anemia likely to respond to steroid therapy include anemias caused by renal insufficiency, sickle cell anemia, refractory anemias

including aplastic anemia, myelofibrosis, myelosclerosis, agnogenic myeloid metaplasia, and anemias caused by malignancy or myelotoxic drugs. The level of response will vary depending on the patient, type of therapy, and form of anemia, but in many cases the management of a normal hematocrit level can be achieved.

In the United States, both oxymetholone (Anadrol 50) and nandrolone decanoate (Deca-Durabolin) are approved by the FDA for the treatment of severe anemia. The guidelines for using oxymetholone with both male and female anemic patients (children and adults) recommend a dosage of 1-2 mg/kg/per day. This would equate to a daily dosage of 75-150 mg for an individual weighing about 160 lbs. Doses as high as 5 mg/kg/day are sometimes necessary to achieve the desired therapeutic response. The guidelines for nandrolone decanoate recommend a dosage of 50-100 mg per week for women and 100-200 mg per week for men. Children (2 to 13 years of age) are recommended a dosage of 25- 50 mg every 3 to 4 weeks.

In recent years, the advent of recombinant erythropoietin as a prescription drug has changed the face of anemia treatment considerably. While anabolic/androgenic steroids still offer therapeutic value here, and are still marketed and sold to treat anemic patients, they are presently regarded as adjunct or fallback medications for use only when therapy with an erythropoietin alone has failed to achieve a desired response. The hematocrit increase from anabolic/androgenic steroids is generally less predictable and positive than the newer erythropoietins, and these drugs also tend to produce very noticeable side effects when given in the levels necessary to stimulate erythropoiesis, especially in women and children. In many instances the risks to therapy strongly outweigh the benefits of anabolic/androgenic steroids, given that there are newer and directly targeted medications available with much lower side effect potential.

### Breast Cancer

Anabolic/androgenic steroids are sometimes prescribed to treat breast cancer in postmenopausal women or premenopausal women who have had their ovaries removed. These drugs are of value when the cancer is hormone responsive, which means that its growth can be affected (positively or negatively) by hormonal manipulation. Androgens and estrogens have opposing actions on hormone-responsive tumors, with estrogens supporting the growth of breast cancer tissue and androgens inhibiting it<sup>67</sup>. The supplementation of an anabolic/androgenic steroid can shift the androgen to estrogen balance in a direction that favors a reduction in

tumor size, a therapy that has elicited a successful response in a fair number of patients. The masculinizing side effects of steroid therapy can be very pronounced in women, however, so therapy is usually initiated with great caution. An oral androgen such as fluoxymesterone is usually preferred to a slower acting injectable steroid such as nandrolone decanoate as well, as it can be abruptly halted if undesirable side effects become too apparent. Both primarily anabolic agents, however, have been widely prescribed for this purpose.

In recent years the development of newer and more targeted anti-estrogenic drugs such as selective estrogen receptor modulators (SERMs) and aromatase inhibiting drugs have almost completely eliminated the use of anabolic/androgenic steroids for breast cancer treatment. Medicative treatment for breast cancer today usually consists of a SERM like Nolvadex (tamoxifen), which may be used with a strong aromatase inhibitor such as Arimidex (anastrozole) or Femara (exemestane). Anabolic/androgenic steroids are still made available in the United States and many other nations for treating breast cancer, and are sometimes still applied. They are very much regarded as adjunct or fallback medications, however, for use only when therapy with anti-estrogenic drugs alone has failed to achieve a desired response.

### **Decreased Fibrinolytic Activity**

Anabolic steroids may be prescribed to treat conditions associated with decreased fibrinolytic activity. Fibrinolysis is the process in which a blood clot is broken down and metabolized by the body. It represents a counter to blood coagulation, with the two systems working together to maintain the hemostatic balance. Disorders of the fibrinolytic system are rare, although can be very serious in nature when they do occur. Decreased fibrinolytic activity can result in a shift in blood clotting factors that greatly favor coagulation (hypercoagulability), increasing the risk of a serious cardiovascular event such as thromboembolism, heart attack, or stroke. Oral C-17 alpha alkylated anabolic steroids are recognized to increase fibrinolytic activity, and as a result have been beneficial in many patients suffering from decreased fibrinolytic activity linked to Antithrombin III deficiency or fibrinogen excess.<sup>68 69</sup> Stanozolol has been most commonly used in the United States for this treatment, although similar therapeutic benefits can be seen with many other anabolic steroids. The maintenance dose is tailored to the individual, and is determined with close monitoring of both side effects and changes to blood coagulation parameters. Esterified injectables and oral non-alkylated steroids do not produce the same fibrinolytic response.<sup>70</sup>

### **Infertility (Male)**

In a small percentage of cases, anabolic/androgenic steroids may be prescribed for the treatment of male infertility. When the cause of infertility is low sperm concentration due to Leydig-cell secretion deficiencies, an androgen might be able to alleviate the condition. In such cases the steroid may increase the sperm count, sperm quality and the fructose concentration,<sup>71 72</sup> which can increase the chance of conception. The oral androgen mesterolone (Proviron) is most commonly prescribed for this purpose, although has not been granted FDA approval for sale in the United States. Note that anabolic/androgenic steroids usually reduce male fertility, so the potential for these agents to successfully treat male fertility is limited.

### **Growth Failure**

Anabolic steroids may be prescribed to treat growth failure in children, both with and without growth hormone deficiency. These agents have been shown to have positive effects on both muscle and bone mass. When they are administered before the ends of the long bones (epiphysis) have fused and further linear growth has been halted, their anabolic effects on bone may support an increase in height.<sup>73</sup> This can occur both through direct anabolic action of the steroid on bone cells, and indirectly via the stimulation of growth hormone and IGF-1 release.<sup>74</sup> An anabolic steroid that is non-aromatizable and non-estrogenic is typically used for this purpose, as estrogen is known to cause an acceleration of growth arrest. Anabolic steroid therapy must always be used with caution in pediatric patients, however. In addition to the possibility of common adverse effects, even non-aromatizable steroids may accelerate the rate of epiphysis closure.<sup>75</sup>

In the United States, oxandrolone is the anabolic steroid most widely prescribed for the treatment of growth failure. It is usually given as a supportive medication, used to augment the anabolic effects of human growth hormone therapy. The drug is typically taken for periods of 6-12 months at a time, in an effort to accelerate the growth rate without substantially affecting the rate of epiphysis fusion. A dosage of 2.5 mg per day is often used for this purpose, although this may be adjusted upwards or downwards depending on the patient's sex, age, bodyweight, and sensitivity to adverse effects. When used under optimal conditions, the result may be an enhancement of the growth rate and an increase in total height compared to not initiating therapy. This benefit has been difficult to achieve consistently in clinical studies, however. A number of trials with oxandrolone have failed to produce a statistically significant effect on total height,

## Steroid Side Effects

While anabolic/androgenic steroids (AAS) are generally regarded as therapeutic drugs with high safety, their use can also be associated with a number of adverse cosmetic, physical, and psychological effects. Many of these side effects are often apparent during therapeutic-use conditions, although their incidence tends to increase profoundly as the dosages reach suprathreshold ranges. Virtually everyone that abuses anabolic/androgenic steroids for physique- or performance-enhancing purposes notices some form of adverse effects from their use. According to one study, the exact frequency of tangible side effects in a group of steroid abusers was 96.4%. This shows very clearly that it is far more rare to abuse these drugs and not notice side effects than it is to endure them.<sup>90</sup> In addition to the side effects that anabolic/androgenic steroids can have on various internal systems, there are others which may not be immediately apparent to the user. The following is a summary of the biological systems and reactions effected by AAS use.

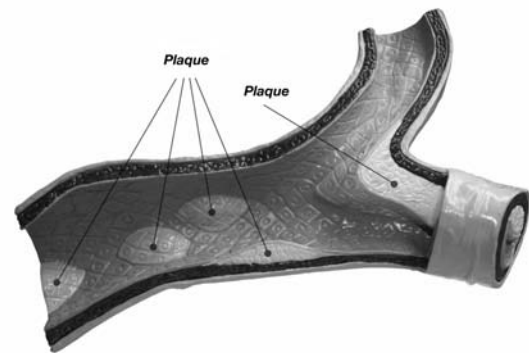
### Cardiovascular System

The use of anabolic/androgenic steroids in suprathreshold (and often therapeutic) doses can have a number of adverse effects on the cardiovascular system. This may be noticed in several areas including unfavorable alterations in serum cholesterol, a thickening of ventricular walls, increased blood pressure, and changes in vascular reactivity. In an acute sense these drugs are admittedly very safe. The risk of an otherwise healthy person suffering a heart attack from an isolated steroid cycle is extremely remote. The risk of stroke is also extremely low. When these drugs are abused for long periods, however, their adverse effects on the cardiovascular system are given time to accumulate. An increased chance of early death due to heart attack or stroke is, likewise, a valid risk with long-term steroid abuse. In order to better understand this risk, we must look specifically at how anabolic/androgenic steroids affect the cardiovascular system in several key ways.

#### Cholesterol/Lipids

Anabolic/androgenic steroids use can adversely affect both HDL (good) and LDL (bad) cholesterol values. The ratio of HDL to LDL cholesterol fractions provides a rough snapshot of the ongoing disposition of plaque in the arteries, either favoring atherogenic or anti-atherogenic actions. The general pattern seen during steroid use is a lowering of HDL concentrations, which is often combined

with stable or increased LDL levels. Triglyceride levels may also increase. The shift can be unfavorable in all directions. Note that in some cases, the total cholesterol count will not change significantly. The total cholesterol level can, therefore, give a false representation of uncompromised lipid health. Almost invariably the underlying HDL/LDL ratio will decrease. While this ratio should return to normal following the cessation of steroid intake, plaque deposits in the arteries are more permanent. If unfavorable shifts in lipids are exacerbated by the long-term use of steroidal compounds, significant damage to the cardiovascular system can result.



**Over time, plaque deposits may begin to narrow and clog arteries.**

Anabolic/androgenic steroids are most consistent in their lowering of HDL levels. This adverse effect is mediated through the androgenic stimulation of hepatic lipase, a liver enzyme responsible for the breakdown of HDL (good) cholesterol.<sup>91</sup> With more hepatic lipase activity in the body, the favorable (anti-atherogenic) HDL cholesterol particles are cleared from circulation more quickly, and their levels drop. This is an effect that seems to be very pronounced at even modest suprathreshold dosage levels. For example, studies with testosterone cypionate noted a 21% drop in HDL cholesterol with a dosage of 300 mg per week.<sup>92</sup> Increasing this dosage to 600 mg did not have any significant additional effect, suggesting that the dosage threshold for strong HDL suppression is fairly low.

Oral steroids, especially c-17 alpha alkylated compounds, are particularly potent at stimulating hepatic lipase and suppressing HDL levels. This is due to first pass concentration and metabolism in the liver. A drug like

stanozolol may, therefore, be milder than testosterone with regard to androgenic side effects, but not when it comes to cardiovascular strain. A study comparing the effects of a weekly injection of 200 mg testosterone enanthate to only a 6 mg daily oral dose of stanozolol demonstrates the strong difference between these two types of drugs very well.<sup>93</sup> After only six weeks, 6 mg of stanozolol was shown to reduce HDL and HDL-2 cholesterol levels by an average of 33 and 71% respectively. HDL levels (mainly the HDL-3 subfraction) were reduced by only 9% in the testosterone group. LDL cholesterol levels also rose 29% with stanozolol, while they dropped 16% with testosterone. Esterified injectable steroids are generally less stressful to the cardiovascular system than oral agents.

It is also important to note that estrogens can have a favorable impact on cholesterol profiles. The aromatization of testosterone to estradiol may, therefore, prevent a more dramatic change in serum cholesterol. A study examined this effect by comparing the lipid changes caused by 280 mg of testosterone enanthate per week, with and without the aromatase inhibitor testolactone.<sup>94</sup> Methyltestosterone was also tested in a third group, at a dose of 20 mg daily, to judge the comparative effect of an oral alkylated steroid. The group using only testosterone enanthate in this study showed a small but not significant decrease in HDL cholesterol values over the course of the 12-week investigation. After only four weeks, however, the group using testosterone plus the aromatase inhibitor displayed an HDL reduction of an average of 25%. The group taking methyltestosterone experienced the strongest HDL reduction in the study, which dropped 35% after four weeks. This group also noticed an unfavorable rise in LDL cholesterol levels.

The potential positive effect of estrogen on cholesterol values also makes the issue of estrogen maintenance something to consider when it comes to health risks. To begin with, one may want to consider whether or not estrogen maintenance drugs are actually necessary in any given circumstance. Are side effects apparent, or is their use a preventative step and perhaps unnecessary? The maintenance drug of choice can also have a measurable impact on cholesterol outcomes. For example, the estrogen receptor antagonist tamoxifen citrate does not seem to exhibit anti-estrogenic effects on cholesterol values, and in fact tends to increase HDL levels in some patients. Many individuals decide to use tamoxifen to combat estrogenic side effects instead of an aromatase inhibitor for this reason, particularly when they are using steroids for longer periods of time, and are concerned about their cumulative cardiovascular side effects.

## **Enlarged Heart**

The human heart is a muscle. It possesses functional androgen receptors, and is growth-responsive to male steroid hormones. This fact partly accounts for men having a larger heart mass on average than women.<sup>95</sup> Physical activity can also have a strong effect on the growth of the heart. Resistance exercise (anaerobic) tends to increase heart size by a thickening of the ventricular wall, usually without an equal expansion of the internal cavity. This is known as concentric remodeling. Endurance (aerobic) athletes, on the other hand, tend to increase heart size via expansion of the internal cavity, without significant thickening of the ventricles (eccentric remodeling). Even with concentric or eccentric remodeling, diastolic function usually remains normal in the athletic heart. The heart muscle is also dynamic. When regular training is removed from a conditioned athlete, the wall thickening and cavity expansion tend to reduce.

Anabolic steroid abusers are at risk for thickening of the left and right ventricular walls,<sup>96</sup> known as ventricular hypertrophy. Hypertrophy of the left ventricle (the main pumping chamber) in particular is extensively documented in anabolic/androgenic steroid abusers.<sup>97</sup> While left ventricular hypertrophy is, again, also found in natural power athletes, substance-abusing athletes tend to have a much more profound wall thickening. They also tend to develop pathological issues related to this thickening, including impaired diastolic function, and ultimately reduced heart efficiency.<sup>98</sup> The level of impairment is closely associated with the dose and duration of steroid abuse. A left ventricle wall exceeding 13mm in thickness is rare naturally, and may be indicative of steroid-abuse or other causes.<sup>99</sup> It may further suggest that pathological left ventricular hypertrophy has developed. Additional testing of such patients is recommended.

Left ventricular hypertrophy (LVH) is an independent predictor of mortality in overweight individuals with high blood pressure.<sup>100</sup> It has also been linked to atrial fibrillation, ventricular arrhythmia, and sudden collapse and death.<sup>101</sup> While LVH in non-steroid-using athletes tends to be without clinical significance, pathological increases in QT dispersion are noticed in steroid abusers with LVH.<sup>102</sup> These changes tend to be similar to the increases in QT dispersion noted in hypertensive patients with LVH.<sup>103</sup> Among other things, this could leave a steroid abusing individual more susceptible to a serious adverse event, including arrhythmia or heart attack. Isolated medical case studies of longtime steroid abusers support an association between LVH and related pathologies including ventricular tachycardia (arrhythmia originating in the left ventricle), left ventricular hypokinesis

(weakened contraction of the left ventricle), and decreased ejection fraction (reduced pumping volume and efficiency).<sup>104</sup>

Heart mass can increase or decrease in relation to the current state of anabolic/steroid use, the average dosage, and duration of intake. Likewise, the heart usually begins to reduce in size once anabolic/androgenic steroids are no longer being used. This effect is similar to the way the heart will reduce in size once an athlete no longer follows a rigorous training schedule.<sup>105</sup> Even with this effect, however, some changes in heart muscle size and function caused by the drugs may persist. Studies examining the effects of steroid use and withdrawal on left ventricular hypertrophy noted that athletic subjects who abstained from steroid abuse for at least several years still had a slightly greater degree of concentric left ventricular hypertrophy compared to non-steroid-using athletic controls.<sup>106</sup> The disposition of pathological left ventricular hypertrophy following long-term steroid abuse and then abstinence remains the subject of investigation and debate.

### **Heart Muscle Damage**

Anabolic/androgenic steroid abuse is suspected of producing direct damage to the heart muscle in some cases. Studies exposing heart cell cultures to AAS have reported reduced contractile activity, increased cell fragility, and reduced cellular (mitochondrial) activity, providing some support for a possible direct toxic effect to the heart muscle.<sup>107 108</sup> Furthermore, a number of case reports have found such pathologies as myocardial fibrosis (scar tissue buildup in the heart), myocardial inflammation (inflammation of heart tissue), cardiac steatosis (accumulation of triglycerides inside heart cells), and myocardial necrosis (death of heart tissue) in long-term steroid abusers.<sup>109 110 111 112</sup> A direct link between drug abuse and cardiac pathologies is assumed in these cases, but cannot be proven given the slow nature in which these cardiac pathologies develop, and the influence many other factors (such as diet, exercise, lifestyle, and genetics) can have on them. Individuals remain cautioned about the possibility of cardiac muscle damage with long-term steroid abuse.

### **Blood Pressure**

Anabolic/androgenic steroids may elevate blood pressure. Studies of bodybuilders taking these drugs in suprathreshold doses have demonstrated increases in both systolic and diastolic blood pressure readings.<sup>113</sup> Another study measured the average blood pressure reading in a group of steroid users to be 140/85, which was compared to 125/80 in weight lifting controls not

taking steroids.<sup>114</sup> Hypertension, or consistently high blood pressure at or above 140/90 for either systolic or diastolic measures, has been reported in steroid users,<sup>115</sup> although in most cases the elevations are more modest. Increased blood pressure may be caused by a number of factors, including increased water retention, increased vascular stiffness, and increased hematocrit. Aromatizing or highly estrogenic steroids tend to cause the greatest influences over blood pressure, although elevations cannot be excluded with non-estrogenic anabolic/androgenic steroids. Blood pressure tends to normalize once anabolic/androgenic steroids have been discontinued.

### **Hematological (Blood Clotting)**

Anabolic/androgenic steroids can cause a number of changes in the hematological system that affect blood clotting. This effect can be very variable, however. The therapeutic use of these drugs is known to increase plasmin, antithrombin III, and protein S levels, stimulate fibrinolysis (clot breakdown), and suppress clotting factors II, V, VII, and X.<sup>116 117</sup> These changes all work to reduce clotting ability. Prescribing guidelines for anabolic/androgenic steroids warn of potential increases in prothrombin time, a measure of how long it takes for a blood clot to form.<sup>118</sup> If prothrombin time increases too greatly, healing may be impaired. The effects of anabolic/androgenic steroids on prothrombin time are generally of no clinical significance to healthy individuals using these drugs in therapeutic dosages. Patients taking anticoagulants (blood thinners), however, could be adversely affected by their use.

Conversely, anabolic/androgenic steroid abuse has been linked to increases in blood clotting ability. These drugs can elevate levels of thrombin<sup>119</sup> and C-reactive protein,<sup>120</sup> as well as thromboxane A2 receptor density,<sup>121</sup> which can support platelet aggregation and the formation of blood clots. Studies of steroid users have demonstrated statistically significant increases in platelet aggregation values in some subjects.<sup>122</sup> There are also a growing number of case reports where (sometimes fatal) blood clots, embolisms, and strokes have occurred in steroid abusers.<sup>123 124 125 126 127</sup> Although it has been difficult to conclusively link these events directly to steroid abuse, the adverse effects of anabolic steroids on components of the blood coagulation system are well understood. These serious adverse effects are now regarded as recognized risks of steroid abuse among many that study these drugs.

In therapeutic levels, the anti-thrombotic effects of anabolic/androgenic steroids seem to dominate physiology, and decreases in blood clotting ability may be

noted. At a certain suprathreshold dosage point, however, the pro-thrombic changes appear to overtake the anti-thrombic changes, and physiology begins to favor fast and abnormally thick clot formation (hypercoagulability). The exact dosage threshold or conditions required to increase blood clotting has not been determined, and some studies with steroid users taking supraphysiological doses fail to demonstrate increased coagulability.<sup>128</sup> Individuals remain warned of the potential increases in thrombic risk with anabolic/androgenic steroid abuse. Blood clotting tendency should return to the pretreated state after the discontinuance of anabolic/androgenic steroids.

### **Hematological (Polycythemia)**

Anabolic/androgenic steroids stimulate erythropoiesis (red blood cell production). One potential adverse effect of this is polycythemia, or the overproduction of red blood cells. Polycythemia can be reflected in the hematocrit level, or the percentage of blood volume that is made up of red cells. As the hematocrit rises, so too does the viscosity of the blood. If the blood becomes too thick, its ability to circulate becomes impaired. This can greatly increase the risk of serious thrombic event including embolism and stroke. A high hematocrit level is also an independent risk factor for heart disease.<sup>129</sup> The normal hematocrit level in men is 40.7 to 50.3%, and in women it is 36.1 to 44.3% (numbers may vary very slightly depending on the source). For the sake of scale, while a hematocrit of 50% may be normal, a hematocrit of 60% or above is considered critical (life threatening).

Anabolic/steroid administration tends to raise the hematocrit level by several percentage points, sometimes more. As a result, many steroid-using bodybuilders will have hematocrit levels that are above the normal range. For example, one study measured the average hematocrit in a group of steroid abusing competitive bodybuilders to be 55.7%.<sup>130</sup> This level is considered clinically high, and would increase blood viscosity enough to raise the risk of serious cardiovascular event. Although not likely to be an isolated cause, high hematocrit is believed to have been a contributing factor in the deaths of a number of steroid abusers, usually paired with high blood pressure, homocysteine, and/or atherosclerosis. The average hematocrit level in bodybuilders not taking anabolic/androgenic steroids was 45.6%, well within the normal range for healthy adult men.

Many physicians that specialize in hormone replacement therapy consider a hematocrit level of 55% to be an absolute cutoff point. At or above this point, and anabolic/androgenic steroid therapy cannot be continued safely. Drug intake would be ceased at this

point until the hematocrit issues have been corrected. Minor elevations in hematocrit may be addressed with phlebotomy. For this, 1 pint of blood may be removed periodically during steroid intake, often every two months. Proper hydration is also important, as dehydration can temporarily cause the hematocrit level to elevate, giving a false positive for polycythemia. The daily intake of aspirin is also commonly advised if the hematocrit is above normal, as this will reduce platelet aggregation, or the tendency for platelets to stick together and form clots. Individuals remain cautioned of the potential cardiovascular danger of high hematocrit levels associated with anabolic/androgenic steroid use.

### **Homocysteine**

Anabolic/androgenic steroids may elevate homocysteine levels. Homocysteine is an intermediary amino acid produced as a byproduct of methionine metabolism. High levels of homocysteine have been linked to elevations in the risk for cardiovascular disease.<sup>131</sup> It is believed to play a direct role in the disease, increasing oxidative stress, including the oxidation of LDL cholesterol, and accelerating atherosclerosis.<sup>132</sup> Elevated levels of homocysteine may also induce vascular cell damage, support platelet aggregation, and increase the likelihood of thrombic event.<sup>133 134 135</sup> The normal range for homocysteine levels in men aged 30 to 59 years is 6.3-11.2umol/L. For women of the same age the average is 4.5-7.9umol/L. Increased risk of heart attack, stroke, or other thrombic event are noted with even modest elevations in homocysteine. According to one study, a homocysteine level exceeding 15umol/L in patients with heart disease is associated with a 24.7% increased likelihood of death within five years.<sup>136</sup>

Androgens stimulate elevations in homocysteine,<sup>137</sup> and men have an approximately 25% higher level on average than women.<sup>138</sup> Anabolic/androgenic steroid abuse has been associated with hyperhomocysteinemia, or consistent clinically high homocysteine levels.<sup>139</sup> One study found that the average homocysteine concentration in a group of 10 men that had been self-administering anabolic/androgenic steroids (in a cyclic pattern) for 20 years was 13.2 umol/L.<sup>140</sup> Three of these men died of a heart attack during the investigation, and had homocysteine levels between 15umol/L and 18umol/L. The average homocysteine level in bodybuilders who had never taken steroids was 8.7umol/L, while it was 10.4umol/L in previous steroid users (3 months abstinence). One study did show that administering 200 mg of testosterone enanthate (with and without an aromatase inhibitor) for three weeks failed to produce a significant elevation in homocysteine.<sup>141</sup> It is unknown if the moderate dosage, drug type (esterified

injectable vs. c17-aa), or short duration of intake were factors in the differing outcome from other studies. Individuals remain warned of the potential for elevations in the homocysteine level with steroid abuse.

**Vascular Reactivity**

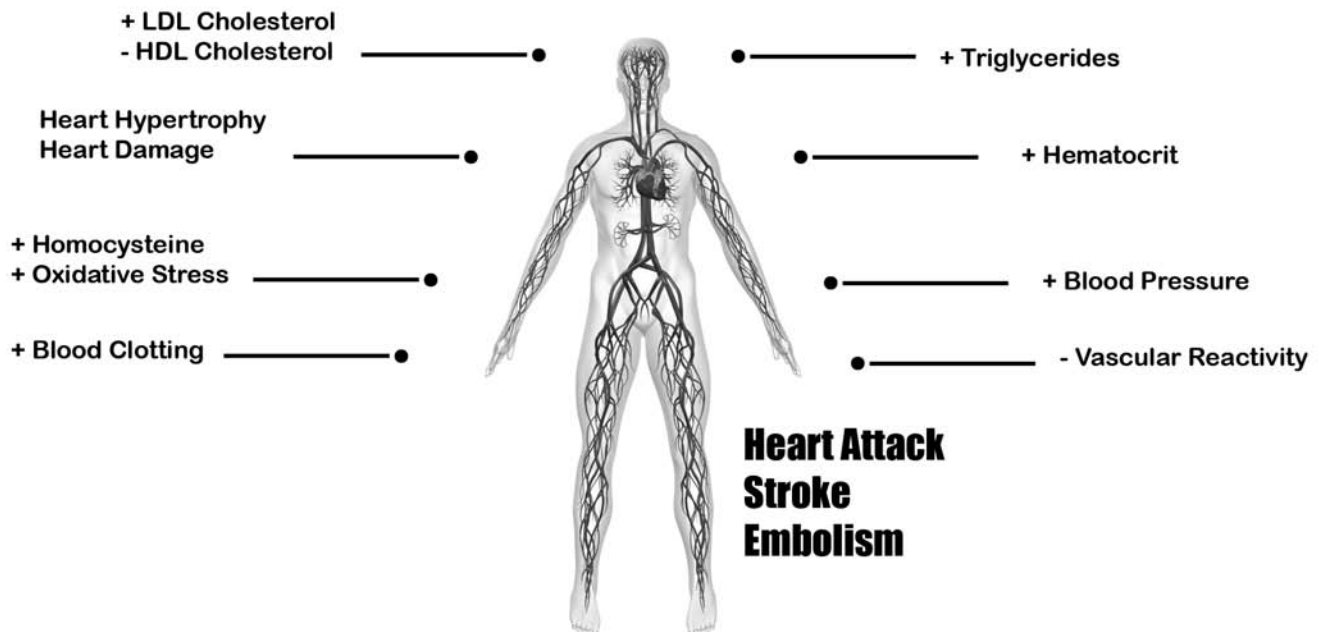
The endothelium is a layer of cells that line the entire circulatory system. These cells are found on the inside of all blood vessels, and help increase or decrease blood flow and pressure by relaxing or constricting the vessels (referred to as vasodilation and vasoconstriction, respectively). These cells also help regulate the passage of materials in and out of blood vessels, and are involved in a number of important vascular processes including blood clotting and new blood vessel formation. Having a more flexible (reactive) endothelium is generally considered desirable for health, and, likewise, the endothelium is often compromised in individuals with cardiovascular disease. Patients with endothelial dysfunction tend to notice greater vasoconstriction, restricted blood flow, higher blood pressure, local inflammation, and reduced circulatory capacity.<sup>142</sup> This may place them at greater risk for heart attack, stroke, or thrombosis (blood clot).

Endothelial cells are androgen responsive, which may partly account for men exhibiting less vascular reactivity than women.<sup>143</sup> Similarly, anabolic/androgenic steroid use has been shown to impair endothelial activity and

vascular reactivity. Studies at the University of Innsbruck in Austria compared the level of endothelial dilation in 20 steroid users to a group of control athletes.<sup>144</sup> Those individuals using anabolic steroids noticed slight but measurably impaired vascular dilation and endothelial function. Additional studies at the University of Wales in Cardiff comparing vascular dilation in active, previous, and non-steroid users, also demonstrated anabolic steroids to cause a decline in endothelial-independent vasodilation.<sup>145</sup> These effects leave the steroid user with more relative "stiffness" in the vascular system, which could increase the chance of an adverse cardiovascular event. In both studies, vascular reactivity improved after the discontinuance of anabolic/androgenic steroids.

**Proving an Association**

Direct links between steroid abuse and individual cases of stroke and heart attack have been difficult to prove. There are a number of things that have made this difficult. For one, cardiovascular disease is very common in men. It also usually takes decades to develop. This makes individual contributing factors (which include many things such as diet, lifestyle, health status, and genetic variables) extremely difficult to isolate. Data concerning the long-term use of steroids in physique- or performance-enhancing doses is also very limited. It would be unethical to conduct a controlled study where participants were given abusive doses of steroids for many years, so the data



**Anabolic/androgenic steroid abuse can produce changes in a number of areas of cardiovascular health that can work together to increase the risk of heart attack, stroke, or embolism.**

## The Endocrinology of Muscle Growth

The road to anabolic insight must include a biological understanding of what muscle growth actually entails. Often simplified by the term “protein synthesis,” muscle growth is actually a highly complex process involving much more than just building proteins from amino acids. Muscle hypertrophy, the correct scientific term for the way we adult humans build skeletal muscle, actually requires the fusion of new cells (called satellite cells) with existing muscle fibers. Since this discovery of satellite cells in 1961, a great deal of research into the mechanisms of muscle hypertrophy has been undertaken. Scientists have come to understand that unlike normal muscle cells, these satellite cells can be regenerated throughout adult life. Furthermore, they serve not as functional units of their own, but provide some of the necessary components to repair and rebuild damaged muscle cells. These satellite cells are normally dormant, and sit resting in small indentations on the outer surface of the muscle fibers, waiting for something to trigger them into activation.

Injury or trauma will provide the stimulus necessary to *activate* satellite cells. Once activated, they will begin to divide, multiply, and form into myoblasts (myoblasts are essentially donor cells that express myogenic genes). This stage of hypertrophy is often referred to as satellite cell *proliferation*. The myoblasts will then fuse with existing muscle fibers, donating their nuclei. This stage of the process is usually called *differentiation*. Skeletal muscle cells are multinucleated, which means they possess many nuclei. Increasing the number of nuclei allows the cell to regulate more cytoplasm, which allows more actin and myosin, the two dominant contractile proteins in skeletal muscle, to be produced. This increases the overall cell size and protein content of the muscle cell. Incidentally, the number of nuclei in relation to cross-sectional area also helps to determine the fiber type of the cell, namely slow twitch (aerobic) or fast twitch (anaerobic)<sup>332 333</sup>. It is important to note that we are not increasing muscle cell number with muscle hypertrophy. We are only increasing cell size and protein content, even though we are using satellite cells to help accomplish this. It is possible for myoblasts to fuse together and actually form new muscle fibers. This is called muscle hyperplasia, and equates to the legitimate growth of new muscle tissue. This is, however, not the primary mechanism of muscle growth in adult life.

### The Anabolic Chain

Now that we know what muscle hypertrophy is really about, let's look at anabolic stimulus and ongoing

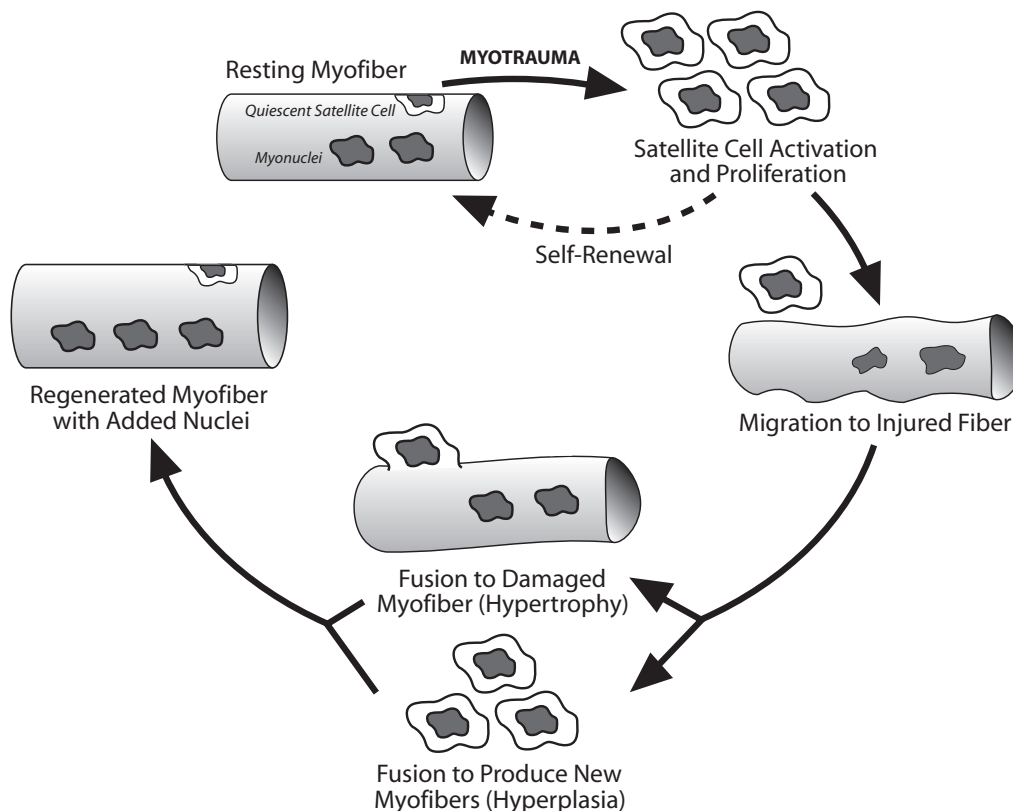
regulation. The following is a rundown of the chain of hormones and growth factors that mediate muscle growth, from the initiation of damage, to final recovery, repair, and growth. For the sake of organization, I have presented them in what I consider to be three logical phases of action. These are not scientifically accepted definitions. Additionally, we could continue to go deeper and deeper into each of the various compounds, messengers, binding proteins, and receptors involved in this intricate and amazing biological activity. I believe the included text will demonstrate the process of muscle anabolism in a very tangible way, however, without too much unnecessary information. Each of the key areas of this section can be further researched for more detail if you are interested. For one so inclined, the medical references in the endnotes would be an excellent place to start.

### Trigger

We all understand that weight training is fundamental to growing muscle tissue. To date, no “sit on your ass and get huge and ripped” pill has been invented. The reason is that a number of changes take place in your local muscle tissues during intense training that are vital to the growth process. Without these early changes, growth is difficult if not impossible to stimulate. So for our purposes, we will start here. Training is the “trigger” in the anabolic process. More specifically, it is the localized cellular damage that weight training produces that will first set us down the road of anabolism. The body will respond by repairing this damage, and in the process will try to adapt by making itself stronger. Muscle growth is always a circular process, with a step back (damage) being necessary to take any steps forward.

### Phase I: Initial Response

The Initial Response phase covers those changes in muscle chemistry that begin immediately, during training, which will lay the groundwork for later repair and growth. In many regards, the Initial Response Phase will control the potential magnitude of other signals to follow. In the anabolic process, this phase is categorized by the release of arachidonic acid from muscle cells, and the formation of active messengers including prostaglandins, cytokines, leukotrienes, and prostacyclins. This begins with the breakdown of the outer phospholipid layer of muscle cells, which is initiated by the cellular disruption of damaging exercise.<sup>334</sup> Phospholipases are released in



#### MUSCLE HYPERTROPHY AND THE 4 STAGES OF THE SATELLITE CELL CYCLE

During the *Activation* stage, dormant satellite cells are stimulated to enter the cell cycle. *Proliferation* marks the formation of new myoblasts (active donor cells). These myoblasts will fuse with existing damaged muscle fibers during the *Differentiation* phase. This allows for greater protein synthesis and the expansion of cell size. *Quiescence* marks the return to a dormant state, where the inactive satellite cells will again rest on the outer layer of the fibers. *Myostatin*, a known inhibitor of muscle growth, is believed to be a key regulator in this stage.<sup>335 336</sup>

response to this trauma, which causes some of the phospholipids stored in the outer layer of the muscle cells to be released. The eccentric part of the exercise movement is of particular importance here, which is the “negative” part of the lift, where the muscle is stretched under resistance.

The amount of arachidonic acid, which is the central bioactive lipid in the anabolic process, liberated will largely control what occurs during this phase. Arachidonic acid is converted locally and immediately via enzymes to a number of active anabolic end products, the most notable of which (in terms of muscle growth) are prostaglandins, which are produced via interaction with cyclooxygenase enzymes. These prostaglandins (PGE2 and PGF2alpha mainly) will control much of the next phase, identified here as the Localized Tissue Priming phase. Additionally, the prostaglandin PGE2 will work to increase local nitric oxide levels, which is also an active molecule in the anabolic process. It has such actions as

dilating blood vessels (to increase the flow of nutrients and hormones to the muscles) and increasing the production of HGF (hepatocyte growth factor) for satellite cell activation. Arachidonic acid contributes to inflammation and pain signaling as well, and its release plays an integral role in the soreness that follows a productive bout of training.

Training intensity and the relative density of arachidonic acid in the phospholipid layer (arachidonic acid availability is ultimately the rate-limiting step in the formation of anabolic prostaglandins) will dictate how much of this potent lipid can be liberated during exercise. The amount of arachidonic acid stored in skeletal muscle tissue is also in a state of constant flux. A number of factors are involved with its regulation, the most notable of which are dietary intake and daily utilization. Regular resistance training depletes arachidonic acid stores, replacing it with other, more abundant, fatty acids.<sup>337</sup> With less arachidonic acid available, the responsiveness of the prostaglandin

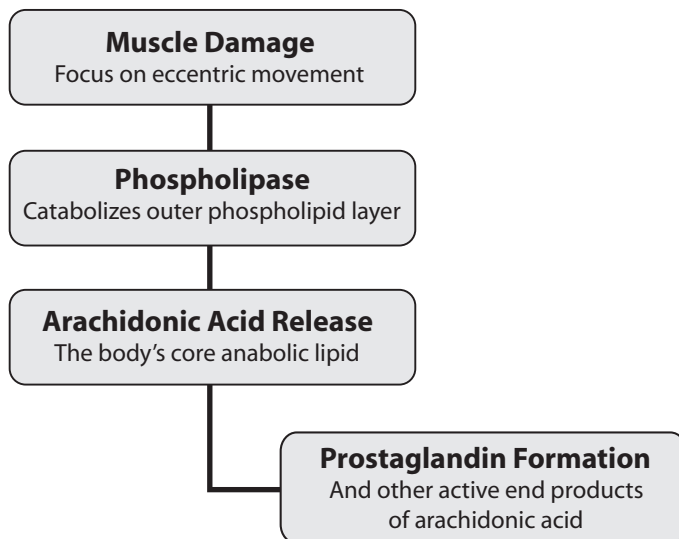
system to regular exercise starts to diminish.<sup>338</sup> *Have you ever wondered why you were so sore when you first start training, or after you took a long break? Or why those early workouts tended to be so much more productive than later ones, where you struggle to notice even moderate soreness?* Much of this is directly tied to your arachidonic acid stores. The more arachidonic acid you have, the easier it is to liberate during training, and vice versa. Thankfully, levels can be augmented with dietary intervention (for more information, see the arachidonic acid profile).

## Phase II: Localized Tissue Priming

Phase II is characterized by a localized increase in growth factor expression and tissue sensitivity to anabolic hormones. Those who have always wondered why anabolic drugs do not work without training will find a good explanation right here. Simply put, your muscles need to be primed for the actions of these drugs first. One way the body accomplishes this is to increase the density of certain receptors in those specific muscles (fibers really) where it needs to initiate repair. This includes, among others, androgen, IGF-1, MGF, and insulin receptors. Stretch-induced muscle damage and the Phase I response are both principle triggers here. Receptor density regulation is important because it prevents anabolic hormones from stimulating tissue growth in areas of the body that do not require it. Receptor density can, therefore, be as strong a regulating force on the pharmacological activity of anabolic drugs as the serum levels of the drugs themselves.

To put it in perspective, we need to remember that there are two separate components that interact before any message is sent to a muscle cell telling it to increase growth. We have a hormone or growth factor on one hand, such as testosterone, IGF-1, MGF, or insulin, and its corresponding receptor on the other. Injecting exogenous anabolic drugs facilitates greater receptor binding and anabolic signaling by providing more messenger hormones/growth factors (obviously). The more hormones or growth factors you have around the cell, the more binding and activation of receptor sites will take place. We cannot forget, however, that having more receptor sites (instead of more hormones) can also facilitate the process too. More receptors mean the existing hormones or growth factors will find them faster. Faster binding means the anabolic message is sent more quickly, and once completed that the anabolic messenger will be more likely to find another receptor site (to send another message) before it is broken down by enzymes. It is all about how much signal can be sent in a given time period, and both sides of the equation are equally important in determining this.

While on one hand we have an increase in tissue sensitivity to anabolic hormones and growth factors, also vital during the Localized Tissue Priming phase is an increase in the localized expression of certain vital growth factors themselves. This includes IGF-1, MGF, FGF, HGF, TNF, IL-1, and IL-6. These compounds will be released, and will work together on the existing damaged muscle fibers and satellite cells, in a sort of grand symphony of muscle anabolism, with each playing its own vital role in the



**Note: Inhibition of the cyclooxygenase-2 enzyme with anti-inflammatory drugs like ibuprofen, acetaminophen, or aspirin, prevents the formation of active prostaglandins. The anabolic cascade is stalled without sufficient prostaglandin formation (Am J Physiol Endocrinol Metab 282:E551-6), interfering with the normal increase in protein synthesis rates after exercise. It is often advised to use such drugs only when necessary if muscle growth is a key focus.**

process. In many cases, the actions of one compound will support the other, either by enhancing its levels, suppressing restricting binding proteins, or supporting its signaling via intertwined mechanisms. A detailed roadmap to all such interactions would go well beyond the scope of this book, and in fact are as of yet not even fully understood to science. A general overview of what is going on with each compound itself, however, is provided in our review of Phase III.

### Phase III: Repair

Your local muscle tissues are primed during Phases I and II. During Phase III, the hormones and growth factors go to work to finish the job. We categorize this phase as one of ongoing anabolic action, action mediated by the combined effects of many anabolic hormones and growth factors including androgens, insulin, IGF-1, IGF-2, MGF, FGF, HGF, TNF, IL-1, and IL-6. This is the time when repair and hypertrophy are physically taking place in your muscles, and each compound will play an intricate role in the process. We must not forget, however, that everything leading up to this point (the actions in Phase I & II) has still been determining how strong the growth response will be, via modifying receptor densities and hormone/growth factor expression. We will follow the individual actions of the anabolic components very closely here. During the third phase, tissue repair and growth will be finalized with the help of the following hormones and growth factors.

**Hepatocyte Growth Factor (HGF):** HGF is a heparin-binding growth factor that resides on the outer surface of uninjured cells. Upon injury, it migrates to satellite cells where it triggers their activation and entry into the cell cycle.<sup>339</sup> HGF expression is regulated via nitric oxide release,<sup>340</sup> which is stimulated upon injury to also aid in the flow of nutrients and hormones to the area. PGE2 plays a pivotal role in nitric oxide synthesis and HGF release.<sup>341</sup>

**Androgens:** Androgens (the hormones that anabolic/androgenic steroids mimic) are strong supporters of protein synthesis rates in skeletal muscle tissue. They are also known to stimulate local IGF-1 expression, so the effects of these hormones extend to the satellite cell cycle (perhaps explaining why they are such strong stimulators of muscle growth). It is also of note that arachidonic acid increases androgen receptor density in skeletal muscle tissue. This helps to further piece together the biochemical links between the Phase I and Phase II response.

**Insulin-Like Growth Factor I (IGF-I):** IGF-I is an insulin-like hormone with marked anabolic effects. Owing to its name, it also has some insulin-like effects as well. IGF-I

increases protein synthesis, and supports the proliferation and differentiation of satellite cells. The prostaglandin PGF2alpha is known to strongly up-regulate local IGF-I receptor expression.<sup>342 343</sup> PGE2 is also believed to play a role in increasing local IGF-1 synthesis.<sup>344</sup>

**Insulin-Like Growth Factor II (IGF-II):** IGF-II is a second insulin-like growth factor that plays a role in the proliferation of satellite cells. Unlike IGF-I, IGF-II expression does not appear to drastically increase in response to training.<sup>345</sup>

**Mechano-Growth Factor (MGF):** Mechano-Growth Factor is a recently discovered variant of Insulin-Like Growth Factor I. This growth factor is produced during an alternate splicing sequence of the IGF protein, and plays a strong role in the support of myoblast proliferation. MGF expression, like many of the growth factors discussed here, is strongly up-regulated in muscle tissue in response to stretch stimulus.<sup>346</sup>

**Fibroblast Growth Factor (FGF):** FGF is actually a family of growth factors, with nine different isoforms (FGF-1 through FGF-9). The full role that FGF plays in muscle hypertrophy in adulthood is not fully understood, however, it is believed to be a strong proliferator of satellite cells, serving to expand their population.<sup>347</sup> FGF's may also play a role in cell differentiation. As with many growth factors, FGF expression up-regulation is proportional to the degree of tissue damage.<sup>348</sup> FGF-2 and FGF-4 seem to be the most prolific representatives of this family in mature muscle tissue.

**Insulin:** In addition to having some ability to increase protein synthesis and inhibit protein breakdown, insulin is the body's chief nutrient transport hormone. The actions of insulin allow cells to transport glucose and amino acids through the plasma membrane. Insulin receptor expression is strongly up-regulated after traumatic exercise, so as to provide more immediate nutrition to the affected area. This up-regulation has been closely linked to the prostaglandin PGE2.<sup>349 350</sup>

**Cytokines (IL-1, IL-6, TNF):** Cytokines are a group of immunomodulatory compounds, though in the context of this section we are loosely referring to them as growth factors. The IL cytokines are called interleukins, and TNF is short for Tumor Necrosis Factor. Among other things, cytokines are known to stimulate the migration of lymphocytes, neutrophils, monocytes, and other healing cells to a site of tissue damage, to aid in cell repair. They help in a number of other ways too, such as aiding in the removal of damaged cells and regulating certain inflammatory responses, including the production of some prostaglandins. Prostaglandins are known to play important roles in the expression of all three of the

cytokines mentioned here,<sup>351 352</sup> however, they may not be the sole stimulus. Other pathways of arachidonic acid metabolism may also be involved.

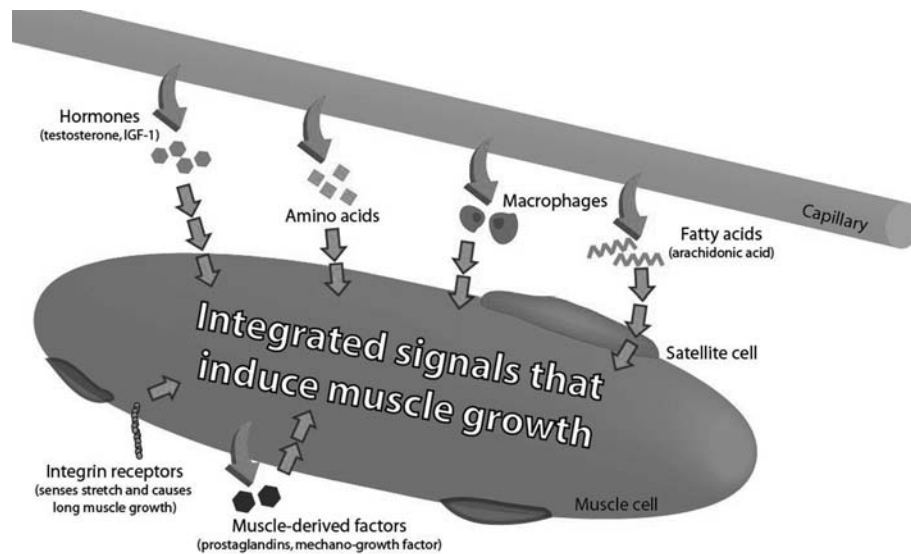
**Prostaglandins:** Although these are the key initial reactionary chemicals, prostaglandins continue to play a role throughout the muscle building process (including Phase III). This includes their support of hormone receptor proliferation, the enhancement of protein synthesis rates, and an intensification of the anabolic signaling of IGF-1 via a shared pathway (PI3K).<sup>353</sup>

**Estrogens:** Although not specifically highlighted in this outline, estrogens also play a minor role in the anabolic process. This includes helping to increase androgen receptor density in certain tissues (though perhaps not skeletal muscle), stimulating the GH/IGF-1 axis, and enhancing glucose utilization for tissue growth and repair.

### Bringing it All Together

So that, in a very loose nutshell, is what is going on inside your body from the time you pick up a weight to the time your muscles are repaired, stronger, and ready for more. If the above seems confusing to you, it should. The fact is, the whole process of muscle growth has been

confounding scientists for decades, and undoubtedly will for decades more. We still have a great way to go before being able to explain fully how it is that muscle hypertrophy occurs in humans. But as you can see, we have traveled a great distance as well. During the mid-1960s, scientists were only first learning that we grow muscle with the help of satellite cells. More than forty years later we have identified, and are experimenting with, dozens of growth factors that were unheard of back then. It is a new world today, and despite not having all the answers, we know enough to enhance human performance in many exciting new ways. But please don't mistake the intention of this section. It is not here to give you a functional roadmap of the entire anabolic process, or to guide you in the ultimate polydrug program. It is here simply to open your mind to the true complexity of anabolism. When we start to see muscle growth from its various angles and intricacies, we begin to see our own potential opportunities for successful exploitation. How many of these opportunities you act upon will depend on your own goals and interests. But no matter how much or how little you actually apply this information, I hope you feel better equipped by having it.



**Skeletal muscle growth is a complex process that involves a variety of signaling compounds.**

## Steroid Cycles

Anabolic/androgenic steroids are not medically approved to promote excessive muscle mass gains (bodybuilding) or improve athletic performance. Aside from early experimentation on athletes by a handful of sports physicians, an extensive effort to study the physique- and performance-enhancing properties of these drugs, specifically with an eye on developing strategies for using them to maximize benefits and minimize adverse effects, has not been undertaken by the medical community. Because of this, illicit users have been left to develop their own protocols for administering these drugs. The result has been a large variety of different approaches to using these agents, some safer or more effective than others. While it would not be possible to comprehensively evaluate all known approaches, this section will discuss some of the most fundamental and time-proven methods for using AAS.

### Steroid Selection

When first considering what steroid(s) to use, one will notice there are many different medications that fall under the category of anabolic/androgenic steroids. This has been the result of many years of development, where specific patients and needs are addressed with drugs that have specific characteristics. For example, some drugs are considered milder (less androgenic), and produce fewer side effects in women and children. Others are more androgenic, which makes them better at supporting sexual functioning in men. Some are injectable medications, and others made for oral administration. There are limits to this diversity, however. All AAS drugs activate the same cellular receptor, and as such share similar protein anabolizing properties. In other words, while different AAS drugs may have some differing properties, if your objective is to gain muscle mass and strength, this could be accomplished with virtually any one of the commercially available agents.

While all AAS drugs may be capable of improving muscle mass, strength, and performance, it would not be correct to say there are no advantages to choosing one agent over another for a particular purpose. Most fundamentally, the quantity and quality of muscle gained may be different from one agent to another. In a general sense, AAS that are also estrogenic tend to be more effective at promoting increases in total muscle size. These steroids also tend to produce visible water (and sometimes fat) retention, however, and are generally favored when raw size is more important than muscle

definition. Drugs with low or no significant estrogenicity tend to produce less dramatic size gains in comparison, but the quality is higher, with greater visible muscularity and definition. In reviewing the most popular AAS drugs, we can separate them into these two main categories as follows.

### Mass (Bulking):

Methandrostenolone – Oral

Oxymetholone – Oral

Testosterone (cypionate, enanthate) – Injectable

### Lean Mass:

Boldenone undecylenate – Injectable

Methenolone enanthate – Injectable

Nandrolone decanoate – Injectable

Oxandrolone – Oral

Stanozolol – Oral

The early stages of AAS use usually involve cycles with a single anabolic/androgenic steroid. Building muscle mass is the most common goal, and usually entails the use of one of the more androgenic substances such as testosterone, methandrostenolone, or oxymetholone. Those looking for lean mass often find favor in such anabolic staples as nandrolone decanoate, oxandrolone, or stanozolol. First time users rarely welcome injecting anabolic/androgenic steroids, and will usually choose an oral compound for the sake of convenience. Methandrostenolone is the most common choice for mass building, and is almost universally regarded as highly effective and only moderately problematic (in terms of estrogenic or androgenic side effects). Stanozolol is the oral anabolic steroid most often preferred for improving lean mass or athletic performance.

The potential for adverse reactions should also be considered when choosing a steroid to use, especially if AAS use is to be regularly repeated. For example, the listed oral medications present greater strain on the

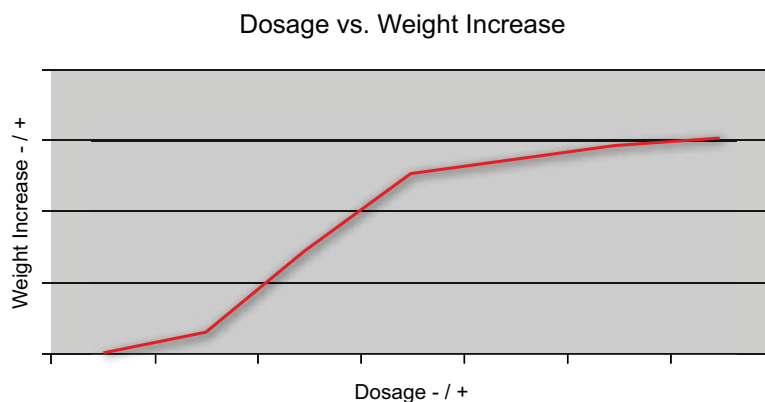
cardiovascular system, and are also liver toxic. For these reasons, the injectable medications listed are actually preferred for safety (testosterone most of all). Potential cosmetic side effects may also be taken into account. For example, men with a strong sensitivity to gynecomastia sometimes prefer non-estrogenic drugs such as methenolone, stanozolol, or oxandrolone. Individuals worried about hair loss, on the other hand, may isolate their use to predominantly anabolic drugs, such as nandrolone, methenolone, and oxandrolone. A detailed review of personal goals, health status, and potential side effects of each drug is advised before committing to any AAS regimen.

## Dosage

The dosage used is important in determining the level of benefit received. Anabolic/androgenic steroids tend to be most efficient at promoting muscle gains when taken at a moderately suprathreshold dosage level. Below this (therapeutic), potential anabolic benefits are often counterbalanced, at least to some extent, by the suppression of endogenous testosterone. At very high doses (excessive suprathreshold), smaller incremental gains are noticed (diminishing returns). In the case of testosterone enanthate or cypionate, for example, a dosage of 100 mg per week is considered therapeutic, and is generally insufficient for noticing strong anabolic benefits. When the dosage is in the 200-600 mg per week range, however, the drug is highly efficient at supporting muscle growth (moderate suprathreshold). Above this range, a greater level of muscle gain may be noticed, but the amount will be small in comparison to the dosage increase. Below are some commonly recommended dosages for the steroids listed earlier.

- Boldenone undecylenate: 200-400 mg/wk
- Methandrostenolone: 10-30 mg/day
- Methenolone enanthate: 200-400 mg/wk
- Nandrolone decanoate: 200-400 mg/wk
- Oxandrolone: 10-30 mg/day
- Oxymetholone: 50-100 mg/day
- Stanozolol: 10-30 mg/day
- Testosterone (cypionate, enanthate): 200-600 mg/wk

There are additional considerations other than the cost effectiveness of a particular dosage. To begin with, high doses of anabolic/androgenic steroids tend to produce stronger negative cosmetic, psychological, and physical side effects. In light of diminishing returns, the tradeoff between results and adverse reactions becomes less and less favorable. Gains made on lower doses also tend to be better retained after steroid discontinuance than those resulting from excessive intake. It is generally not realistic to expect that rapid double-digit weight gains induced by massive dosing will remain long after a cycle is over. Slower steadier gains are advised. It is also very important to remember that higher doses aren't always what are needed to achieve greater gains. An individual more focused on his or her training and diet will often make better gains on lower dosages of AAS than a less dedicated individual taking higher doses. With this understanding, AAS should only be considered when all other variables of training and diet have been addressed, and always limited to the minimum dosage necessary to achieve the next realistic training/performance goal.



**Figure 1. Anabolic/androgenic steroids tend to be most effective in moderately suprathreshold doses. The anabolic benefits diminish in relation to the amount of drug given at both the high and low ends of the dosage range.**

## Duration (Cycling)

The administration of anabolic/androgenic steroids at a given dosage will typically produce noticeable increases in muscle size and strength for approximately 6-8 weeks. After this point, the rate of new muscle gain typically slows significantly. A plateau may be reached soon after, where all forward momentum has ceased. To continue making significant progress beyond this point can entail escalating dosages, which is likely to coincide with a greater incidence of adverse reactions and diminishing anabolic returns. Even without dosage escalation, negative health changes are already likely to be apparent, and should be corrected fairly quickly. The practice of extended or continuous steroid administration is discouraged for these reasons. It is generally recommended to use AAS drugs for no longer than 8 weeks at a time (10-12 weeks at the maximum), followed by an equal or longer period of abstinence before another steroid regimen is initiated. This pattern of rotating between "on" and "off" periods is referred to as cycling.

## Off-Cycle (Recovery, Bridging, and Tapering)

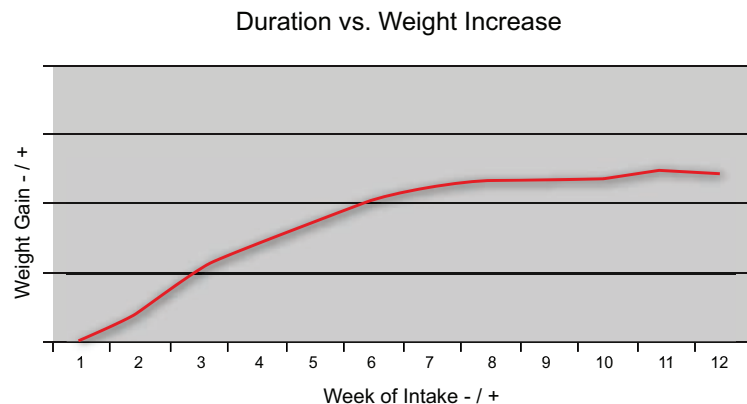
The period immediately following steroid cessation can involve a state of hypogonadism (low androgen levels), and as a result protein catabolism. In an effort to minimize muscle loss, the objective here is usually on restoring natural testosterone production, maintaining an optimal level of muscle stimulation, and remaining dedicated to proper nutrition. A hormonal recovery program is usually initiated, which may involve the use of HCG, tamoxifen, and clomiphene (see PCT: Post Cycle Therapy). A substantial off-cycle period is also advised, involving abstinence from anabolic/androgenic steroids for at least

8-12 weeks. Some AAS abusers have difficulties with complete drug abstinence, and will initiate "bridging" routines between full-dose cycles. This may involve the periodic low-dose administration of an injectable steroid, such as 200 mg of testosterone enanthate or methenolone enanthate every 2-3 weeks. Such practice is discouraged, however, as it can interfere with hormonal recovery, and prevent a return to metabolic homeostasis.

When concluding a cycle, some steroid users also follow a practice of first slowly reducing their dosages (tapering). This tapering may proceed for a 3-4 week period, and will involve an even stepping down of the dose each week until the point of drug discontinuance. It is unknown, however, if such tapering offers any tangible value. This practice has never been evaluated in a clinical setting, and is not widely recommended with steroid medications as it is with some other drugs such as thyroid hormones or antidepressants. Virtually every high-dose AAS administration study can also be found to end at the maximum dosage, with no time allotted to tapering. One flaw in the logic of using a tapering program is that they are ostensibly designed to aid hormone recovery. Recovery is not possible, however, while supraphysiological levels of androgens are present, and such levels are usually found during all weeks of a normal (nonmedical) steroid taper. Individuals remain cautioned that dosage tapering is not a proven way to reduce post-cycle muscle catabolism.

## Stacking

As individuals become more experienced with anabolic/androgenic steroid use they may begin experimenting with the use of more than one steroid at a time. This practice is referred to as stacking. Stacking is



**Figure 2. Anabolic/androgenic steroids tend to be most effective at a given dosage for approximately 6-8 weeks. After this point, the rate of new muscle gain will slow, and soon after will usually hit a full plateau.**

most common with advanced bodybuilders who find that at a certain level of physical development they begin hitting plateaus that are difficult to break with a previous single-agent approach. In many cases, however, it may simply be the greater cumulative steroid dosage that is necessary for the resumed progress. Stacking usually involves the combination of a more androgenic steroid with one or more primarily anabolic agents. On the anabolic side, common steroids of choice include boldenone, methenolone, nandrolone, oxandrolone, and stanozolol. Testosterone, oxymetholone, or methandrostenolone will serve as the androgenic base of most stacks.

The reasons for stacking androgenic and anabolic steroids together in this manner are two fold. On the one hand, high doses of testosterone, oxymetholone, or methandrostenolone are prone to producing strong androgenic and estrogenic side effects. Stacking first became very popular during the 1960s, a time when effective estrogen maintenance drugs were not widely available. An anabolic-androgen stack allowed the use of a higher total steroid dosage than would be tolerable with a single androgen. Anabolic-androgen pairing also appears to offer efficacy advantages over the use of primarily anabolic agents alone, even when they are taken in higher doses. This conflicts with the original expectations for "anabolic" steroids, which were

specifically designed to emphasize muscle-building properties, but is repeatedly noticed by users. The reason the basic androgenic steroids are more anabolically productive is not fully understood, but is believed to involve the interplay of estrogenic hormones, androgenic stimulation in the central nervous system, and potentially other unidentified synergisms necessary for optimal muscle growth.

Today, the availability of drugs that can reduce estrogenic activity makes the continued use of single agent cycles based on a strong androgen like testosterone enanthate or cypionate much more viable than it was decades ago. Side effects like gynecomastia and water retention can now be effectively minimized with anti-estrogens or aromatase inhibitors, even when taking higher doses. Individuals should be aware that stacking is, likewise, not a necessary practice. It is likely to remain commonly applicable in competitive bodybuilding circles, however, or when an individual is sure they have progressed as far as they possibly can with a single-agent approach. Otherwise, for many athletes and recreational bodybuilders, the periodic use of a single steroid will be more than sufficient to maintain optimal levels of muscle mass and performance, and it may never be necessary to deviate from this approach.

## Harm Reduction / Safer Use Guidelines

Harm reduction is a concept among healthcare workers that seeks to reduce the negative health consequences of drug abuse. The principles of harm reduction call for an acceptance of the fact that, good or bad, illicit drugs exist in today's society. Instead of ignoring drug users, harm reduction practitioners actively work with them to promote safer use strategies and decrease the health damage of drug abuse. The effort of harm reduction is always helping, not judging, the individual. Although previously focused exclusively on narcotic drugs of abuse,

harm reduction principles can (and should) also be developed for steroid users, a group that rarely has the benefit of full physician oversight in its drug programs. In an effort to further this goal, ANABOLICS has outlined the following principles of steroid harm reduction. If followed, these principles should measurably reduce the negative health impact of steroid use, making it a safer (although not completely safe) practice.

### Principles of Anabolic Steroid Harm Reduction

**1. Avoid Counterfeit and Underground Steroids.** Anabolic steroids produced by illicit manufacturers are often of low quality, and may present additional health risks to the user beyond what are presented by the steroids themselves. Even if they contain actual steroids in properly labeled doses, underground drugs may contain toxic heavy metals, use dirty raw materials, or even carry bacterial, viral, and other forms of contamination. Pharmaceutical drug purity is assured to the public only by an extremely costly, tedious, and methodical process of quality assurance and government oversight. There is little financial and even logistical incentive for most underground drug makers to produce their drugs at such high levels of purity. Counterfeit and underground drugs are not considered equal substitutes for real pharmaceutical products, and should be avoided.

**2. Avoid Toxic Oral Steroids.** Aside from Andriol, Primobolan, and Proviron, every oral steroid discussed in this reference book is a c-17 alpha alkylated compound and should be avoided whenever possible. While there may be a number of clinical reasons to prescribe such a drug, when used in the higher doses necessary for muscle growth these agents tend to have significant negative impacts on certain health markers. Their most notable effect is to increase the ratio of LDL (bad) to HDL (good) cholesterol in the body, which favors increased plaque deposition in the

arteries. Over time this may increase the risk of heart disease. C-17 alpha alkylated steroids are also the drugs exclusively associated with strong liver stress and (rarely) liver cancer. If injection can be tolerated, and moderate physique or performance improvement is the goal, all of the same results can be achieved without oral steroids. Note that injectable forms of otherwise oral steroids (such as stanozolol and methandrostenolone) should also be avoided, as they provide a similar level of hepatic and cardiovascular strain regardless of the differing route of administration.

**3. Think of Testosterone First.** Of all the anabolic/androgenic steroids produced, testosterone esters like cypionate, enanthate, and Sustanon tend to have the lowest negative impact on health when taken in muscle building and performance-enhancing doses. Testosterone drugs provide a hormone identical to that already produced in the body, presenting the same spectrum of physical and physiological effects. In addition to being one of the most efficient muscle-builders available, testosterone generally has a positive (not negative) effect on libido, supports a positive mood, and supplements necessary estrogen so that cholesterol levels are less negatively shifted. The exclusive use of testosterone drugs for body or performance enhancement is advised if possible.

**4. Limit Yourself to the "Safest" Drugs.** If the exclusive use of an injectable testosterone is not feasible, limiting use to the safest group of steroids is advised. Of the injectable class, the following drugs have the lowest cardiovascular strain and are recommended: Deca-Durabolin (nandrolone decanoate), Durabolin (nandrolone phenylpropionate), Equipoise (boldenone undecylenate), and Primobolan Depot (methenolone enanthate). If an oral steroid is desired, only Andriol, Primobolan, or Proviron should be used. These drugs are not c-17 alpha alkylated, and can all provide additional steroid activity without the same level of cardiovascular and hepatic strain seen with other common oral steroids including Anadrol (oxymetholone), Anavar (oxandrolone), Dianabol (methandrostenolone), and Winstrol (stanozolol).

**5. Use Health Support Supplements.** Anabolic/androgenic steroid users can help lower the negative health impact of steroid use with the consumption of natural health support supplements. To begin with, the negative cardiovascular effects of these drugs can be offset (at least to some degree) with cholesterol supplements. Fish oil is recommended as a base, which should be stacked with a number of other clinically studied cholesterol support ingredients including green tea, garlic powder, resveratrol, phytosterols, niacin, and policosinol. The blended product Lipid Stabil (Molecular Nutrition) includes these ingredients and is recommended. Cholesterol support supplements should be taken at all times during anabolic steroid therapy. Next, those taking oral steroids should be reducing liver strain with a liver support supplement. Recommended products include Liver Stabil (Molecular Nutrition), Liv-52 (Himalaya Drug Company), and Essentiale Forte (Aventis). One of these products should be taken at all times during therapy with hepatotoxic agents

**6. Always Cycle Steroids.** A steroid cycle usually consists of 6 to 12 weeks of drug use followed by an equal period of time or more abstaining from all anabolic/androgenic steroids. This practice is advised for a number of reasons. For one, as you supplement male steroid hormones your body will reduce the production of its own testosterone. Cycling helps reduce the risk of

developing long-term fertility and hormonal issues, which are sometimes caused by the uninterrupted use of steroids for many months or years. Cycling also lets your general markers of health (such as cholesterol levels, hematocrit, and blood pressure) return to their normal state periodically, reducing the impact temporary changes may have over time. Those individuals who use anabolic/androgenic steroids for long periods of time without interruption run a greater risk that these negative changes in health markers will result in long-term health issues.

**7. Use Reasonable Dosages.** High doses of steroids are not necessary to achieve significant muscle growth, especially if moderate physique or performance enhancement is desired. A dosage limit of 400 mg per week on injectables is advised. In the case of testosterone cypionate, 400 mg per week equates to at least 4 to 5 times the level of hormone naturally produced in a healthy male body. This level of use will produce dramatic muscle gain if combined with proper training and diet. In fact, during the 1970s and 80s the dosage range of 200-400 mg per week was considered "standard" for the bodybuilding use of testosterone, nandrolone, boldenone, or methenolone. There is actually little real need for extreme doses of 750-1,000 mg or more of steroid per week, or to supplement an injectable base with additional orals. High doses may produce a faster rate of gain, but are generally not cost effective for the extra muscle they provide. Additionally, high doses of steroids greatly increase cardiovascular strain and the incidence of other side effects.

**8. Avoid Aromatase Inhibitors.** Aromatase-inhibiting drugs counter estrogenic side effects by preventing the production of estrogen in the body. While an effective practice, they also deprive the body of a hormone that is important to cardiovascular health. In particular, estrogen supports the production of good (HDL) cholesterol, which means that aromatase inhibitors may inadvertently increase the cardiovascular strain of a steroid cycle. If estrogenic side effects are apparent and a reduction or elimination of the offending steroid(s) is not considered an option, the SERM (Selective Estrogen Receptor Modulator) drug Nolvadex could be used instead. This drug offers

partial estrogenic action in the liver, which may allow it to counter estrogenic side effects without the same negative shift in cholesterol.

**9. Get Regular Blood Tests.** Comprehensive blood testing including an examination of hormones, cholesterol, blood cell concentrations, and enzymes is the most useful tool for assessing the negative health impact of steroid use. Changes in cholesterol, for example, can help quantify for the user what effect a particular drug regimen is having on their cardiovascular health. The individual then has the opportunity to better assess long-term risk if this cycle is to be repeated. At a minimum, blood testing should be conducted before a cycle is initiated, 3 to 4 weeks into a cycle, and a couple of months after a cycle. This allows for 1) a baseline for later comparison; 2) a snapshot of the on-cycle health impact; and 3) an opportunity to assess if natural homeostasis has been restored post-cycle.

**10. Use Proper Injection Procedures.** Careful attention to correct injection procedures can help eliminate some of the complications associated with nonmedical steroid use. Steroids are given via deep intramuscular injections. The most common site of application is the upper outer quadrant of the gluteus muscle, although the drugs are also commonly injected to the upper outer thigh and shoulder. Site injections (in smaller muscle groups like the biceps, triceps, or calf muscles) for cosmetic purposes are discouraged, as they are technically more difficult to navigate and more prone to complications. Comfortable injection volumes should also be used, generally no more than 3 mL per application. Each injection site should be rotated so that the same muscle is not injected more than once every two weeks. A general focus should be made on cleanliness, including the use of alcohol pads on the vials and skin before injection, and the proper disposal of all needles and empty vials/ampules after use.

**11. Sterilize.** Though never advised, should the choice be made to use an injectable steroid of underground origin, an effort should be made to sterilize the solution before use. This will reduce the likelihood of illness or infection due to microorganism.

**12. Watch Your Diet.** Anabolic/androgenic steroids can allow an individual significantly more latitude with their diet than normal. The caloric demand typically increases due to the effects of these drugs on muscle mass and metabolism, allowing more calories to be consumed each day without adding fat mass. It is important not to let this latitude affect your health in a negative way. Remember, the use of steroids at physique- and performance-enhancing doses is expected to cause an unfavorable shift in cholesterol levels and other cardiovascular health markers, favoring a higher risk of cardiovascular disease. Simultaneously feeding your body greater amounts of saturated fats, cholesterol, and simple carbohydrates can make the impact of these drugs even worse. Diets low in saturated fats, cholesterol, and simple sugars are recommended, and are known to reduce cardiovascular disease risk. Note, however, that diet alone is not effective at countering the negative cardiovascular effects of steroid use, but dietary restrictions can reduce these risks.

**13. Always Consider Reward AND Risk.** It can be easy to ignore the potential health impact of steroid use when the positive benefits are so rapid and the negative consequences so remote. At the end of the day, however, it is very important to remember that the use of steroids in doses sufficient to support short term muscle gain are virtually always going to have some negative impact on your body. Your cholesterol will shift in an unfavorable direction, your blood pressure may go up a little bit, and you may ever so slightly thicken the ventricles in your heart. Your hormones are out of balance when you take steroids, which will invariably cause other things to go out of balance. Steroid use is rarely dangerous over a short term period. These hormonal drugs are acutely very safe. As use continues over the years, however, these short-term periods accumulate, and total on-cycle time may become very long. Always remember to consider the risks as well as the rewards of each cycle. Choosing your drug program carefully and keeping the negative effects of steroid use in check over the short term is the best way to reduce long term risks.

## Counterfeit Steroid Identification

This section pertains to methods for differentiating between legitimate pharmaceutical products and illegitimate copies (counterfeits). Before we begin, I need to remind you that counterfeiting anabolic steroids is a very lucrative business these days. Counterfeiters are investing a lot of money in printing and packaging equipment so that you'll have a hard time picking out their products. Furthermore, there are now many large "commercial scale" counterfeiting operations, with the capacity to manufacture all product formats including ampules, logo imprinted pills, and push-through tablet strips. Given this high level of sophistication, steroids purchased on the black market need to be inspected with great care. The mistakes made by counterfeiters are often minor, and noticed in the fine (not obvious) detail.

### Step #1: Eliminate the Obvious

When counterfeit steroids first appeared decades ago, they were often very easy to spot. The manufacturers operated on a small scale, and made small-scale mistakes. For example, the printing might be sloppy, or the containers thin and flimsy. They might have lacked the equipment to put the product in a box, or even affix an expiration date and lot number to it. No legitimate pharmaceutical would be sold like this. Much has changed over the years, however. Few counterfeiters still make the basic mistakes that were once common. Don't expect identifying these products to be easy. Still, that is not to say that obvious counterfeits aren't available. Indeed, they can be found on the black market from time to time. This first set of instructions, therefore, seeks to eliminate only the most obvious fakes. For the rest, we will need a more detailed analysis.

**1. Sloppy Printing.** Drug manufacturing is not a small scale endeavor. Sizable pharmaceutical companies control the global drug trade, and make products that are typically very professional in appearance. You should not expect to see things like runny inks, sloppy lines, or misaligned images on real drug packaging. Sometimes counterfeiters still use cheap (small-scale) printing and reproduction methods, which make labels and boxes that stand out as sloppy. Don't ever use a product if it just doesn't "look right" to you. You are probably subconsciously picking up on minor deviations.

**2. Cheap Packaging.** Virtually all legitimate steroid products come in boxes. Inside the box you should find a drug information sheet. Some counterfeiters will skip

these steps entirely. Real ampules, vials, and tablets are sometimes smuggled loose, but let someone else take the risk. The box for a pharmaceutical product should be structurally sound, closing tightly and evenly. Some counterfeiters seal their own boxes by hand, and they may be uneven or poorly glued. Real boxes should be printed (ink directly on cardboard). Some counterfeiters cover plain white boxes with stickers. If the vial, ampule, or bottle has a label, machines should have put it on straight. Counterfeiters often apply labels by hand, so many will be crooked. Some counterfeiters use ampules, but blank laboratory samples. These are filled by hand and sealed over a flame. They are a bit larger than the average ampule, and somewhat unusual in appearance. A good rule of thumb is to avoid any steroid that does not come in a professional looking package.

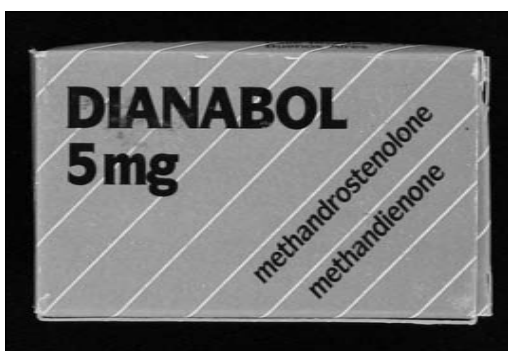
**The ampule [right] is a laboratory blank, meant to be sealed by hand over a flame. It is larger and more unusual in appearance than most traditional ampules.**



**3. Multi-dose Containers.** In the United States, we are used to our injectable medications coming in multi-dose vials (these have a rubber top to let needles pass through more than once), and our pills loose in bottles. Most other countries, however, do not allow this type of packaging for human medicines. They consider it unsterile, and permit it only for animal drugs. Instead, they require each dosage unit to be separate. This usually means break open glass ampules for injectable medications, and push through blisters for pills and capsules. Since you are unlikely to find real American products on the black market, it may be best to avoid all multi-dose containers when it comes to human pharmaceuticals. Most are going to be counterfeit. When you find veterinary drugs in multi-dose containers, extra care should be taken to examine them closely, since these products are more easily counterfeited.



The above is a crude copy of an American testosterone product, which uses the same label on the box and vial. A counterfeit as simple as this is rare to find today.

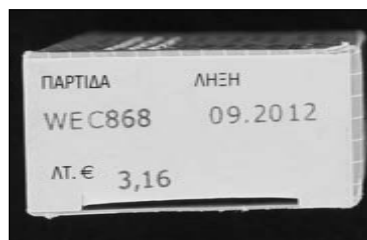


Another example of an obvious counterfeit. This box is crude in design and uses a brand name that has been off the market since the 1980s.

## Step #2: Examine Lot Number/Expiration

A more formal analysis should always begin with the lot number/expiration date. Pharmaceutical companies have their boxes and labels manufactured in bulk, usually at an offsite printing facility. They are not serialized; lot numbers/expiration dates have not yet been applied to them. This information is added with a mechanical stamping machine or computer/inkjet printer at the time the drug is packaged. Counterfeiters often don't wait, and simply print the lot number/expiration date with the rest of the boxes and labels. This means less work, less equipment, and less cost. Knowing this, examining the lot number/expiration date information can be a good way to spot counterfeits. You need to look at the lot/date information very closely, preferably with a handheld microscope with 100-200X magnification.

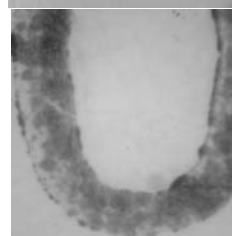
The photographs below show what it looks like when the lot number and expiration date are added after the initial box/label printing, as well as counterfeit products without this feature. The characters on a real pharmaceutical product should stand out from the rest of the printing, which will consist of tiny dots blended together to create a solid image (see Step #3 for more information on the ink). When the lot/expiration information is added with a mechanical stamp, the ink will be much more solid under magnification (note that it may appear blotchy under deep magnification). Depending on the equipment, it may also have left a physical indent you can feel when rubbing your thumb over the information. When the dates were added by computer, we usually see large dots that are visible to the naked eye. Be careful to look at the characters closely. Counterfeiters will try to make the information look like it was added by machine or computer, even though it was printed. If you see that tiny dots make up the characters under 200X magnification, it is not legitimate stamp or computer printing.



Normal



20X

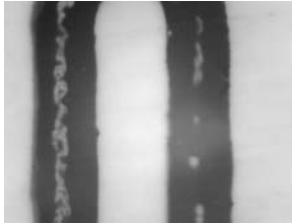


200X

Example #1. A real box of Proviron. Under magnification we can see that the lot number and expiration date were stamped on mechanically.

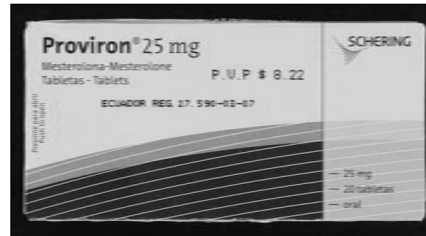


20X

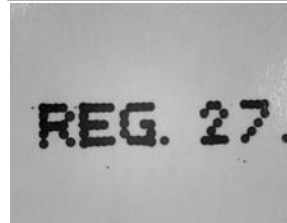


200X

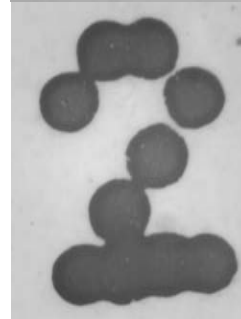
Example #2. Another example of mechanical stamping of the lot number and expiration date.



Normal



20X



200X

Example #4. Another real product (Proviron) with information applied post-printing with a computer printer.



Normal

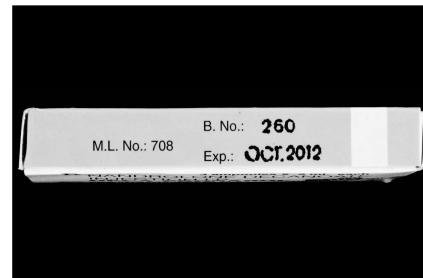


20X

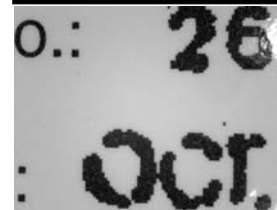


200X

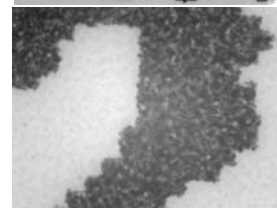
Example #3. Real testosterone cypionate from Watson (U.S.) The above lot/expiration date were added by computer printer. Under magnification we see the large dots are solid ink.



Normal



20X

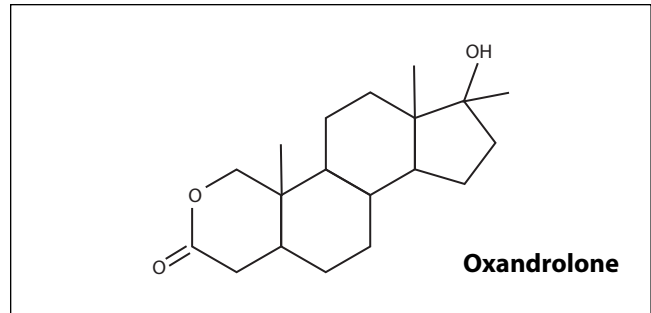


200X

Example #5. (Counterfeit). At first glance the slight run on the ink appears to be the result of mechanical stamping. Under magnification, however, we see this is simulated.

## Anavar (oxandrolone)

<b>Androgenic</b>	24
<b>Anabolic</b>	322-630
<b>Standard</b>	Methyltestosterone (oral)
<b>Chemical Names</b>	17b-hydroxy-17a-methyl-2-oxa-5a-androstane-3-one
<b>Estrogenic Activity</b>	none
<b>Progestational Activity</b>	none



### Description:

Oxandrolone is an oral anabolic steroid derived from dihydrotestosterone. It was designed to have a very strong separation of anabolic and androgenic effect, and no significant estrogenic or progestational activity. Oxandrolone is noted for being quite mild as far as oral steroids are concerned, well tailored for the promotion of strength and quality muscle tissue gains without significant side effects. Milligram for milligram it displays as much as six times the anabolic activity of testosterone in assays, with significantly less androgenicity.<sup>421</sup> This drug is a favorite of dieting bodybuilders and competitive athletes in speed/anaerobic performance sports, where its tendency for pure tissue gain (without fat or water retention) fits well with the desired goals.

### History:

Oxandrolone was first described in 1962.<sup>422</sup> It was developed into a medicine several years later by pharmaceutical giant G.D. Searle & Co. (now Pfizer), which sold it in the United States and the Netherlands under the Anavar trade name. Searle also sold/licensed the drug under different trade names including Lonavar (Argentina, Australia), Lipidex (Brazil), Antitriol (Spain), Anatrophill (France), and Protivar. Oxandrolone was designed to be an extremely mild oral anabolic, one that could even be used safely by women and children. In this regard Searle seems to have succeeded, as Anavar has shown a high degree of therapeutic success and tolerability in men, women, and children alike. During its early years, Anavar had been offered for a number of therapeutic applications, including the promotion of lean tissue growth during catabolic illness, the promotion of lean tissue growth following surgery, trauma, infection, or prolonged corticosteroid administration, or the support of bone density in patients with osteoporosis.

By the 1980's, the FDA had slightly refined the approved applications of oxandrolone to include the promotion of

weight gain following surgery, chronic infection, trauma, or weight loss without definite pathophysiologic reason. In spite of its ongoing track record of safety, Searle decided to voluntarily discontinue the sale of Anavar on July 1, 1989. Lagging sales and growing public concern about the athletic use of anabolic steroids appeared to be at the root of this decision. With the Anavar brand off the market, oxandrolone had completely vanished from U.S. pharmacies. Soon after, oxandrolone products in international markets (often sold by or under license from Searle) began to disappear as well, as the leading global manufacturer of the drug continued its withdrawal from the anabolic steroid business. For several years during the early 1990's, it looked as if Anavar might be on its way out of commerce for good.

It would be approximately six years before oxandrolone tablets would be back on the U.S. market. The product returned to pharmacy shelves in December 1995, this time under the Oxandrin name by Bio-Technology General Corp. (BTG). BTG would continue selling it for the FDA approved uses involving lean mass preservation, but had also been granted orphan-drug status for the treatment of AIDS wasting, alcoholic hepatitis, Turner's syndrome in girls, and constitutional delay of growth and puberty in boys. Orphan drug status gave BTG a 7-year monopoly on the drug for these new uses, allowing them to protect a very high selling price. Many patients were outraged to learn that the drug would cost them (at wholesale price) between \$3.75 and \$30 per day, which was many times more costly than Anavar had been just several years back. The release of a 10 mg tablet from BTG several years later did little to reduce the relative cost of the drug.

Oxandrin® continues to be sold in the U.S., but is now under the Savient label (formerly known as BTG). It is currently approved by the FDA for "adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma and in some patients who without definite pathophysiologic reasons

fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis." Generic versions of the drug are now available in the U.S., which has reduced the price of oxandrolone therapy. Outside of the U.S., oxandrolone remains available, although not widely.

#### **How Supplied:**

Oxandrolone is available in select human drug markets. Composition and dosage may vary by country and manufacturer. The original Anavar brand contained 2.5 mg of steroid per tablet. Oxandrin contains 2.5 mg or 10 mg per tablet. Other modern brands commonly contain 2.5 mg, 5 mg, or 10 mg of steroid per tablet.

#### **Structural Characteristics:**

Oxandrolone is a modified form of dihydrotestosterone. It differs by: 1) the addition of a methyl group at carbon 17-alpha to protect the hormone during oral administration and 2) the substitution of carbon-2 in the A-ring with an oxygen atom. Oxandrolone is the only commercially available steroid with such a substitution to its basic ring structure, an alteration that considerably increases the anabolic strength of the steroid (partly by making it resistant to metabolism by 3-hydroxysteroid dehydrogenase in skeletal muscle tissue).

#### **Side Effects (Estrogenic):**

Oxandrolone is not aromatized by the body, and is not measurably estrogenic. Oxandrolone also offers no related progestational activity.<sup>423</sup> An anti-estrogen is not necessary when using this steroid, as gynecomastia should not be a concern even among sensitive individuals. Since estrogen is the usual culprit with water retention, oxandrolone instead produces a lean, quality look to the physique with no fear of excess subcutaneous fluid retention. This makes it a favorable steroid to use during cutting cycles, when water and fat retention are major concerns. Oxandrolone is also very popular among athletes in strength/speed sports such as sprinting, swimming, and gymnastics. In such disciplines one usually does not want to carry around excess water weight, and may find the raw muscle-growth brought about by oxandrolone to be quite favorable over the lower quality mass gains of aromatizable agents.

#### **Side Effects (Androgenic):**

Although classified as an anabolic steroid, androgenic side effects are still possible with this substance. This may include bouts of oily skin, acne, and body/facial hair growth. Anabolic/androgenic steroids may also aggravate

male pattern hair loss. Women are warned of the potential virilizing effects of anabolic/androgenic steroids. These may include a deepening of the voice, menstrual irregularities, changes in skin texture, facial hair growth, and clitoral enlargement. Oxandrolone is a steroid with low androgenic activity relative to its tissue-building actions, making the threshold for strong androgenic side effects comparably higher than with more androgenic agents such as testosterone, methandrostenolone, or fluoxymesterone.

The low androgenic activity of oxandrolone is due in part to it being a derivative of dihydrotestosterone. This creates a less androgenic steroid because the agent lacks the capacity to interact with the 5-alpha reductase enzyme and convert to a more potent "di-hydro" form. This is unlike testosterone, which is several times more active in androgen responsive target tissues such as the scalp, skin, and prostate (where 5-alpha reductase is present in high amounts) due to its conversion to DHT. In essence, oxandrolone has a more balanced level of potency between muscle and androgenic target tissues. This is a similar situation as is noted with Primobolan and Winstrol, which are also derived from dihydrotestosterone and not known to be very androgenic substances.

#### **Side Effects (Hepatotoxicity):**

Oxandrolone is a c17-alpha alkylated compound. This alteration protects the drug from deactivation by the liver, allowing a very high percentage of the drug entry into the bloodstream following oral administration. C17-alpha alkylated anabolic/androgenic steroids can be hepatotoxic. Prolonged or high exposure may result in liver damage. In rare instances life-threatening dysfunction may develop. It is advisable to visit a physician periodically during each cycle to monitor liver function and overall health. Intake of c17-alpha alkylated steroids is commonly limited to 6-8 weeks, in an effort to avoid escalating liver strain.

Oxandrolone appears to offer less hepatic stress than other c-17 alpha alkylated steroids. The manufacturer identifies oxandrolone as a steroid that is not extensively metabolized by the liver like other 17-alpha alkylated orals, which may be a factor in its reduced hepatotoxicity. This is evidenced by the fact that more than a third of the compound is still intact when excreted in the urine.<sup>424</sup> Another study comparing the effects of oxandrolone to other alkylated agents including methyltestosterone, norethandrolone, fluoxymesterone, and methandriol demonstrated that oxandrolone causes the lowest sulfobromophthalein (BSP; a marker of liver stress) retention of the agents tested.<sup>425</sup> 20 mg of oxandrolone produced 72% less BSP retention than an equal dosage of fluoxymesterone, which is a considerable difference being

that they are both 17-alpha alkylated.

A more recent study looked at escalating doses (20 mg, 40 mg, and 80 mg) of oxandrolone in 262 HIV+ men. The drug was administered for a period of 12 weeks. The group taking 20 mg of oxandrolone per day showed no statistically significant trends of hepatotoxicity in liver enzyme (AST/ALT; aminotransferase and alanine aminotransferase) values. Those men taking 40 mg noticed a mean increase of approximately 30-50% in liver enzyme values, while the group of men taking 80 mg noticed an approximate 50-100% increase. Approximately 10-11% of the patients in the 40 mg group noticed World Health Organization grade III and IV toxicity according to AST and ALT values. This figure jumped to 15% in the 80 mg group. While serious hepatotoxicity cannot be excluded with oxandrolone, these studies do suggest that it is measurably safer than other alkylated agents.

The use of a liver detoxification supplement such as Liver Stabil, Liv-52, or Essentiale Forte is advised while taking any hepatotoxic anabolic/androgenic steroids.

#### **Side Effects (Cardiovascular):**

Anabolic/androgenic steroids can have deleterious effects on serum cholesterol. This includes a tendency to reduce HDL (good) cholesterol values and increase LDL (bad) cholesterol values, which may shift the HDL to LDL balance in a direction that favors greater risk of arteriosclerosis. The relative impact of an anabolic/androgenic steroid on serum lipids is dependant on the dose, route of administration (oral vs. injectable), type of steroid (aromatizable or non-aromatizable), and level of resistance to hepatic metabolism. Oxandrolone has a strong effect on the hepatic management of cholesterol due to its structural resistance to liver breakdown, non-aromatizable nature, and route of administration. In the previously cited study in HIV+ males, 20 mg of oxandrolone daily for 12 weeks caused a mean serum HDL reduction of 30%. HDL values were suppressed 33% in the 40 mg group, and 50% in the 80 mg group. This was accompanied by a statistically significant increase in LDL values (approximately 30-33%) in the 40 mg and 80 mg groups, further increasing atherogenic risk. Anabolic/androgenic steroids may also adversely effect blood pressure and triglycerides, reduce endothelial relaxation, and support left ventricular hypertrophy, all potentially increasing the risk of cardiovascular disease and myocardial infarction.

At one time oxandrolone was looked at as a possible drug for those suffering from disorders of high cholesterol or triglycerides. Early studies showed it to be capable of lowering total cholesterol and triglyceride values in certain types of hyperlipidemic patients, which was

thought to signify potential for this drug as a lipid-lowering agent.<sup>426</sup> With further investigation it was found, however, that any lowering of total cholesterol values was accompanied by a redistribution in the ratio of good (HDL) to bad (LDL) cholesterol that favored greater atherogenic risk.<sup>427 428</sup> This negates any positive effect this drug might have on triglycerides or total cholesterol, and actually makes it a potential danger in terms of cardiac risk, especially when taken for prolonged periods of time. Today we understand that as a group, anabolic/androgenic steroids tend to produce unfavorable changes in lipid profiles, and are really not useful in disorders of lipid metabolism. As an oral c17 alpha alkylated steroid, oxandrolone is even more risky to use in this regard than an esterified injectable such as a testosterone or nandrolone.

To help reduce cardiovascular strain it is advised to maintain an active cardiovascular exercise program and minimize the intake of saturated fats, cholesterol, and simple carbohydrates at all times during active AAS administration. Supplementing with fish oils (4 grams per day) and a natural cholesterol/antioxidant formula such as Lipid Stabil or a product with comparable ingredients is also recommended.

#### **Side Effects (Testosterone Suppression):**

All anabolic/androgenic steroids when taken in doses sufficient to promote muscle gain are expected to suppress endogenous testosterone production. Oxandrolone is no exception. In the above-cited study on HIV+ males, twelve weeks of 20 mg or 40 mg per day caused an approximate 45% reduction in serum testosterone levels. The group taking 80 mg noticed a 66% decrease in testosterone. Similar trends of decrease were noticed in LH production, with the 20 mg and 40 mg doses causing a 25-30% reduction, and the 80 mg group noticing a decline of more than 50%. Additionally, studies on boys with constitutionally delayed puberty have demonstrated significant suppression of endogenous LH and testosterone with as little as 2.5 mg per day.<sup>429</sup> Without the intervention of testosterone stimulating substances, testosterone levels should return to normal within 1-4 months of drug secession. Note that prolonged hypogonadotropic hypogonadism can develop secondary to steroid abuse, necessitating medical intervention.

*The above side effects are not inclusive. For more detailed discussion of potential side effects, see the Steroid Side Effects section of this book.*

**Administration (General):**

Studies have shown that taking an oral anabolic steroid with food may decrease its bioavailability.<sup>430</sup> This is caused by the fat-soluble nature of steroid hormones, which can allow some of the drug to dissolve with undigested dietary fat, reducing its absorption from the gastrointestinal tract. For maximum utilization, this steroid should be taken on an empty stomach.

**Administration (Men):**

The original prescribing guidelines for Anavar called for a daily dosage of between 2.5 mg and 20 mg per day (5-10 mg being most common). This was usually recommended for a period of two to four weeks, but occasionally it was taken for as long as three months. The dosing guidelines recommended with the current U.S. production form of the drug (Oxandrin, Savient Pharmaceuticals) also call for between 2.5 and 20 mg of drug per day, taken in intermittent cycles of 2 to 4 weeks. The usual dosage for physique- or performance-enhancing purposes is in the range of 15-25 mg per day, taken for 6 to 8 weeks. These protocols are not far removed from those of normal therapeutic situations.

Oxandrolone is often combined with other steroids for a more dramatic result. For example, while bulking one might opt to add in 200-400 mg of a testosterone ester (cypionate, enanthate, or propionate) per week. The result should be a considerable gain in new muscle mass, with a more comfortable level of water and fat retention than if taking a higher dose of testosterone alone. For dieting phases, one might alternately combine oxandrolone with a non-aromatizing steroid such as 150 mg per week of a trenbolone ester or 200-300 mg of Primobolan® (methenolone enanthate). Such stacks are highly favored for increasing definition and muscularity. An in-between (lean mass gain) might be to add in 200-400 mg of a low estrogenic compound like Deca-Durabolin® (nandrolone decanoate) or Equipoise® (boldenone undecylenate).

**Administration (Women):**

The original prescribing guidelines for Anavar did not offer separate dosing recommendations for women, although it was indicated that women who were pregnant, or may become pregnant, should not use the drug. The current guidelines for Oxandrin also do not make special dosing recommendations for women. Women who fear the masculinizing effects of many steroids would be quite comfortable using this drug, as these properties are very rarely seen with low doses. For physique- or performance-enhancing purposes, a daily dosage of 5-10 mg should illicit considerable growth without the noticeable androgenic side effects of other

drugs. This would be taken for no longer than 4-6 weeks. Eager females may wish to add another mild anabolic such as Winstrol®, Primobolan® or Durabolin®. When combined with such anabolics, the user should notice faster, more pronounced muscle-building effects, but it may also increase the likelihood of seeing androgenic side effects (or hepatotoxicity in the case of Winstrol).

**Availability:**

Pharmaceutical preparations containing oxandrolone are fairly limited. The drug is unavailable in Europe, and with a handful of exceptions in the west, its production is increasingly being shifted to less regulated markets in Asia. In reviewing some of the remaining products and changes on the global pharmaceutical market, we have made the following observations.

Various forms of generic oxandrolone are now available in the U.S. in both 2.5 mg and 10 mg dosages, from manufacturers such as Par Pharm, Sandoz, Upsher Smith, and Watson.

Brand name Oxandrin is still available in the U.S. under the Savient brand name. It comes in bottles of 60 (10 mg) tablets or 100 (2.5 mg) tablets each.

The generic Italian product Oxandrolone (SPA) is no longer available. It was previously being made for export sales only. There are no remaining oxandrolone products available on the Italian market.

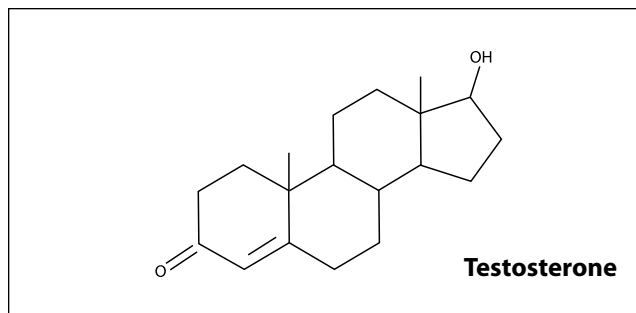
Atlantis (Mexico) produces an oxandrolone product called Xtendrol. It carries 2.5 mg of steroid per tablet, and comes in a box of 30 tablets each.

Asia Pharma makes the product Oxanabolic in Malaysia. It comes in strips of 10 tablets each, 10 strips per box. Each product should carry a unique product ID code that can be verified with the company for authenticity. This product is presently export only, but the manufacturer claims to be in the process of seeking Thai FDA approval.

Balkan Pharmaceuticals (Moldova) makes the product Oxandrolon. It is prepared in 10 mg tablets, with 20 tablets contained in each foil and plastic strip.

## Depo<sup>®</sup>-Testosterone (testosterone cypionate)

<b>Androgenic</b>	100
<b>Anabolic</b>	100
<b>Standard</b>	Standard
<hr/>	
<b>Chemical Names</b>	4-androsten-3-one-17beta-ol 17beta-hydroxy-androst-4-en-3-one
<b>Estrogenic Activity</b>	moderate
<b>Progestational Activity</b>	low



### Description:

Testosterone cypionate is a slow-acting injectable ester of the primary male androgen testosterone. Testosterone is also the principle anabolic hormone in men, and is the basis of comparison by which all other anabolic/androgenic steroids are judged. As with all testosterone injectables, testosterone cypionate is highly favored by athletes for its ability to promote strong increases in muscle mass and strength. It is interesting to note that while a large number of other steroidal compounds have been made available since testosterone injectables, they are still considered to be the dominant bulking agents among bodybuilders. There is little argument that these are among the most powerful mass drugs available, testosterone cypionate included.

### History:

Testosterone cypionate first appeared on the U.S. drug market during the mid-1950's under the brand name of Depo-Testosterone cyclopentylpropionate (soon abridged to simply Depo-Testosterone). It was developed by the pharmaceutical giant Upjohn, and is still sold to this day by the same company under the same trade name (although now they are called Pharmacia & Upjohn). This is a drug with limited global availability, and has historically been (largely) identified as an American item. It is not surprising that American athletes have long favored this form of testosterone over testosterone enanthate, the dominant slow-acting ester of testosterone on the global market. This preference, however, is likely rooted in history and availability, not actual therapeutic advantages.

Testosterone cypionate and testosterone enanthate provide extremely comparable patterns of testosterone release. Not only are physical advantages not possible in one over the other, but actual differences in pharmacokinetic patterns are hard to notice (these two drugs are for all intents and purposes functionally interchangeable). The only key difference between the two

seems to be in the area of patient comfort. Cypionic acid is less irritating at the site of injection than enanthic acid (enanthate) for a small percentage of patients. This makes testosterone cypionate a more favorable choice for those with recurring issues of injection-site pain with testosterone enanthate. This difference likely had something to do with the early development of this testosterone ester as a commercial drug product.

The main use of testosterone cypionate in clinical medicine has historically been the treatment of low androgen levels in males, although many other applications have existed for this drug as well. During the 1960's, for example, the drug's prescribing recommendations called for such uses as supporting bone structure maturity, treating menorrhagia (heavy menstrual bleeding) and excessive lactation in females, and increasing muscle mass and combating osteoporosis in the elderly. It was also being recommended for increasing male fertility, whereby induced testosterone/spermatogenesis suppression (caused by administering 200 mg of testosterone cypionate per week for 6 to 10 weeks) was potentially followed by a period of rebound spermatogenesis (due to temporarily higher than normal gonadotropin levels).

By the 1970's, the FDA had been granted much stronger control over the prescription drug market, and the broad uses in which testosterone cypionate was first indicated were now being refined. For example, "testosterone rebound therapy" as a way to increase male fertility was proving to be unreliable, especially in the face of newer more effective medications, and was soon eliminated from prescribing guidelines. So too was the recommendation for its use to treat things like excessive menstrual bleeding and lactation. In general, testosterone therapy was being pulled back to focus mainly on male androgen deficiency, and less on other applications, especially when involving populations more susceptible to androgenic side effects, such as women and the elderly.

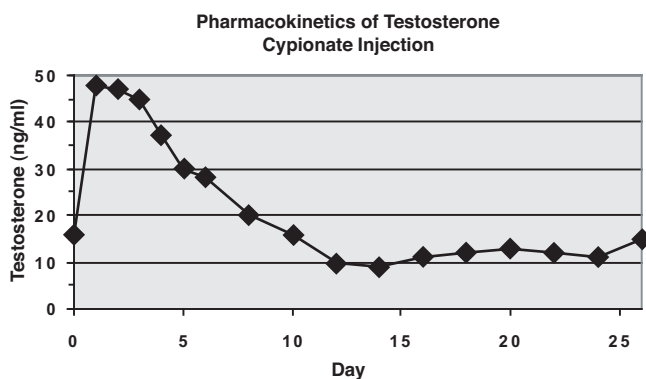
Today, testosterone cypionate remains readily available on the U.S. prescription drug market, where it is FDA-approved for hormone replacement therapy in men with conditions associated with a deficiency of endogenous testosterone, and as a secondary treatment for inoperable metastatic breast cancer in women (although it is not widely used for this purpose anymore). Testosterone cypionate is currently available outside of the United States, but not widely. Known international sources for the drug include Canada, Australia, Spain, Brazil, and South Africa.

#### **How Supplied:**

Testosterone cypionate is available in select human and veterinary drug markets. Composition and dosage may vary by country and manufacturer, but usually contain 50 mg/ml, 100 mg/ml, 125 mg/ml, or 200 mg/ml of steroid dissolved in oil.

#### **Structural Characteristics:**

Testosterone cypionate is a modified form of testosterone, where a carboxylic acid ester (cyclopentylpropionic acid) has been attached to the 17-beta hydroxyl group. Esterified forms of testosterone are less polar than free testosterone, and are absorbed more slowly from the area of injection. Once in the bloodstream, the ester is removed to yield free (active) testosterone. Esterified forms of testosterone are designed to prolong the window of therapeutic effect following administration, allowing for a less frequent injection schedule compared to injections of free (unesterified) steroid. The half-life of testosterone cypionate is approximately 8 days after injection.



**Figure 1. Pharmacokinetics of 200 mg testosterone cypionate injection. Source: Comparison of testosterone, dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone in serum after injection of testosterone enanthate or testosterone cypionate. Schulte-Beerbuhl M, Nieschlag E. Fertility and Sterility 33 (1980):201-3.**

#### **Side Effects (Estrogenic):**

Testosterone is readily aromatized in the body to estradiol (estrogen). The aromatase (estrogen synthetase) enzyme is responsible for this metabolism of testosterone. Elevated estrogen levels can cause side effects such as increased water retention, body fat gain, and gynecomastia. Testosterone is considered a moderately estrogenic steroid. An anti-estrogen such as clomiphene citrate or tamoxifen citrate may be necessary to prevent estrogenic side effects. One may alternately use an aromatase inhibitor like Arimidex® (anastrozole), which more efficiently controls estrogen by preventing its synthesis. Aromatase inhibitors can be quite expensive in comparison to anti-estrogens, however, and may also have negative effects on blood lipids.

Estrogenic side effects will occur in a dose-dependant manner, with higher doses (above normal therapeutic levels) of testosterone cypionate more likely to require the concurrent use of an anti-estrogen or aromatase inhibitor. Since water retention and loss of muscle definition are common with higher doses of testosterone cypionate, this drug is usually considered a poor choice for dieting or cutting phases of training. Its moderate estrogenicity makes it more ideal for bulking phases, where the added water retention will support raw strength and muscle size, and help foster a stronger anabolic environment.

#### **Side Effects (Androgenic):**

Testosterone is the primary male androgen, responsible for maintaining secondary male sexual characteristics. Elevated levels of testosterone are likely to produce androgenic side effects including oily skin, acne, and body/facial hair growth. Men with a genetic predisposition for hair loss (androgenetic alopecia) may notice accelerated male pattern balding. Those concerned about hair loss may find a more comfortable option in nandrolone decanoate, which is a comparably less androgenic steroid. Women are warned of the potential virilizing effects of anabolic/androgenic steroids, especially with a strong androgen such as testosterone. These may include deepening of the voice, menstrual irregularities, changes in skin texture, facial hair growth, and clitoral enlargement.

In androgen-responsive target tissues such as the skin, scalp, and prostate, the high relative androgenicity of testosterone is dependant on its reduction to dihydrotestosterone (DHT). The 5-alpha reductase enzyme is responsible for this metabolism of testosterone. The concurrent use of a 5-alpha reductase inhibitor such as finasteride or dutasteride will interfere with site-specific potentiation of testosterone action, lowering the tendency of testosterone drugs to produce androgenic side effects. It is important to remember that

anabolic and androgenic effects are both mediated via the cytosolic androgen receptor. Complete separation of testosterone's anabolic and androgenic properties is not possible, even with total 5-alpha reductase inhibition.

#### **Side Effects (Hepatotoxicity):**

Testosterone does not have hepatotoxic effects; liver toxicity is unlikely. One study examined the potential for hepatotoxicity with high doses of testosterone by administering 400 mg of the hormone per day (2,800 mg per week) to a group of male subjects. The steroid was taken orally so that higher peak concentrations would be reached in hepatic tissues compared to intramuscular injections. The hormone was given daily for 20 days, and produced no significant changes in liver enzyme values including serum albumin, bilirubin, alanine-amino-transferase, and alkaline phosphatases.<sup>478</sup>

#### **Side Effects (Cardiovascular):**

Anabolic/androgenic steroids can have deleterious effects on serum cholesterol. This includes a tendency to reduce HDL (good) cholesterol values and increase LDL (bad) cholesterol values, which may shift the HDL to LDL balance in a direction that favors greater risk of arteriosclerosis. The relative impact of an anabolic/androgenic steroid on serum lipids is dependant on the dose, route of administration (oral vs. injectable), type of steroid (aromatizable or non-aromatizable), and level of resistance to hepatic metabolism. Anabolic/androgenic steroids may also adversely affect blood pressure and triglycerides, reduce endothelial relaxation, and support left ventricular hypertrophy, all potentially increasing the risk of cardiovascular disease and myocardial infarction.

Testosterone tends to have a much less dramatic impact on cardiovascular risk factors than synthetic steroids. This is due in part to its openness to metabolism by the liver, which allows it to have less effect on the hepatic management of cholesterol. The aromatization of testosterone to estradiol also helps to mitigate the negative effects of androgens on serum lipids. In one study, 280 mg per week of testosterone ester (enanthate) had a slight but not statistically significant effect on HDL cholesterol after 12 weeks, but when taken with an aromatase inhibitor a strong (25%) decrease was seen.<sup>479</sup> Studies using 300 mg of testosterone ester (enanthate) per week for 20 weeks without an aromatase inhibitor demonstrated only a 13% decrease in HDL cholesterol, while at 600 mg the reduction reached 21%.<sup>480</sup> The negative impact of aromatase inhibition should be taken into consideration before such drug is added to testosterone therapy.

Due to the positive influence of estrogen on serum lipids, tamoxifen citrate or clomiphene citrate are preferred to aromatase inhibitors for those concerned with cardiovascular health, as they offer a partial estrogenic effect in the liver. This allows them to potentially improve lipid profiles and offset some of the negative effects of androgens. With doses of 600 mg or less per week, the impact on lipid profile tends to be noticeable but not dramatic, making an anti-estrogen (for cardioprotective purposes) perhaps unnecessary. Doses of 600 mg or less per week have also failed to produce statistically significant changes in LDL/VLDL cholesterol, triglycerides, apolipoprotein B/C-III, C-reactive protein, and insulin sensitivity, all indicating a relatively weak impact on cardiovascular risk factors.<sup>481</sup> When used in moderate doses, injectable testosterone esters are usually considered to be the safest of all anabolic/androgenic steroids.

To help reduce cardiovascular strain it is advised to maintain an active cardiovascular exercise program and minimize the intake of saturated fats, cholesterol, and simple carbohydrates at all times during active AAS administration. Supplementing with fish oils (4 grams per day) and a natural cholesterol/antioxidant formula such as Lipid Stabil or a product with comparable ingredients is also recommended.

#### **Side Effects (Testosterone Suppression):**

All anabolic/androgenic steroids when taken in doses sufficient to promote muscle gain are expected to suppress endogenous testosterone production. Testosterone is the primary male androgen, and offers strong negative feedback on endogenous testosterone production. Testosterone-based drugs will, likewise, have a strong effect on the hypothalamic regulation of natural steroid hormones. Without the intervention of testosterone-stimulating substances, testosterone levels should return to normal within 1-4 months of drug secession. Note that prolonged hypogonadotropic hypogonadism can develop secondary to steroid abuse, necessitating medical intervention.

As with all anabolic/androgenic steroids, it is unlikely that one will retain every pound of new bodyweight after a cycle is concluded. This is especially true when withdrawing from a strong (aromatizing) androgen like testosterone cypionate, as much of the new weight gain is likely to be in the form of water retention, quickly eliminated after drug discontinuance. An imbalance of anabolic and catabolic hormones during the post-cycle recovery period may further create an environment that is unfavorable for the retention of muscle tissue. Proper ancillary drug therapy is usually recommended to help restore hormonal balance more quickly, ultimately

helping the user retain more muscle tissue.

Another way to lessen the post-cycle "crash" is to first replace testosterone cypionate with a milder anabolic such as nandrolone decanoate or methenolone enanthate. The new steroid would be administered alone for one to two more months, at a dosage of 200-400 mg per week. In this "stepping down" procedure the user is attempting to eliminate the watery bulk of a testosterone-based drug while simultaneously preserving the solid muscularity underneath. This practice can prove to be effective, even if mainly for psychological reasons (some may view it as simply dividing the crash into water and hormonal stages). Testosterone-stimulating drugs are still typically used at the conclusion of therapy, as endogenous testosterone production will not rebound during the administration of nandrolone decanoate or methenolone enanthate.

*The above side effects are not inclusive. For more detailed discussion of potential side effects, see the Steroid Side Effects section of this book.*

#### **Administration (Men):**

To treat androgen insufficiency, the prescribing guidelines for testosterone cypionate call for a dosage of 50-400 mg every two to four weeks. Although active in the body for a longer time, testosterone cypionate is usually injected on a weekly basis for physique- or performance-enhancing purposes. The usual dosage is in the range of 200-600 mg per week, taken in cycles 6 to 12 weeks in length. This level is sufficient for most users to notice exceptional gains in muscle size and strength.

Testosterone is usually incorporated into bulking phases of training, when added water retention will be of little consequence, the user more concerned with raw mass than definition. Some do incorporate the drug into cutting cycles as well, but typically in lower doses (100-200 mg per week) and/or when accompanied by an aromatase inhibitor to keep estrogen levels under control. Testosterone cypionate is a very effective anabolic drug, and is often used alone with great benefit. Some, however, find a need to stack it with other anabolic/androgenic steroids for a stronger effect, in which case an additional 200-400 mg per week of boldenone undecylenate, methenolone enanthate, or nandrolone decanoate should provide substantial results with no significant hepatotoxicity. Testosterone is ultimately very versatile, and can be combined with many other anabolic/androgenic steroids to tailor the desired effect.

While large doses are generally not advised, some bodybuilders have been known to use excessively high dosages of this drug (1,000 mg per week or more). This

was much more common before the 1990's, when cypionate vials were usually very cheap and easy to find. A "more is better" attitude is easy to justify when paying only \$20 for a 10cc vial (today the typical price for a single injection). At dosages of 800-1000 mg per week or more, water retention will likely account for more of the additional weight gain than new muscle tissue. The practice of "megadosing" is inefficient (not to mention potentially dangerous), especially when we take into account the typical high cost of steroids today.

#### **Administration (Women):**

Testosterone cypionate is rarely used with women in clinical medicine. When applied, it is most often used as a secondary medication during inoperable breast cancer, when other therapies have failed to produce a desirable effect and suppression of ovarian function is necessary. Testosterone cypionate is not recommended for women for physique- or performance-enhancing purposes due to its strong androgenic nature, tendency to produce virilizing side effects, and slow-acting characteristics (making blood levels difficult to control).

#### **Availability:**

Testosterone cypionate remains widely available as a prescription drug product. Its production is largely associated with American companies, although recently has been expanding into loosely regulated Asian markets that still cater to demand by bodybuilders and athletes. In reviewing some of the products and changes in the global pharmaceutical market, we have made the following observations.

Brand name testosterone cypionate (Depot-Testosterone) remains available in the United States from Prizer. This is a high-profile target of counterfeiters. All legitimate boxes will carry a "Jh" symbol hidden on one of the top inside flaps. It will appear when placed under UV light.

Many generic forms of the drug are also produced in the U.S. market by manufacturers such as Watson, Sandoz, Paddock, Synerx, and Bedford. All come packaged in multiple-dose vials. Due to strict controls these products are rarely diverted for illicit sale. There are also several pharmacies custom-compounding testosterone cypionate for doctors that specialize in androgen replacement therapy.

Cypionax is available in Thailand by T.P. Drug Laboratories. It comes in 2 mL ampules containing 100 mg/mL of steroid.

Cybiobolic from Asia Pharma (Malaysia) is now approved for sale through pharmacies in Thailand. Each box should carry a scratch-off security sticker, which will display a

code that can be validated on the company website.

Testex Prolongatum remains available in Spain. This steroid is produced by Laboratorios Q Pharma. It is packaged in 2 mL dark glass ampules with grey silkscreen lettering. It comes in two doses, containing a total of 100 mg or 250 mg of steroid. Testex has always been a high-profile item for counterfeiters.

Found in Chile is a high-dose cypionate product called ciclo-6. The product is manufactured by the firm Drag Pharma, and contains 300 mg/ml of steroid in a 2 mL ampule (600 mg of cypionate in total).

Balkan Pharmaceuticals (Moldova) makes the product Testosterona C. It is prepared in both 1 mL ampules and multi-dose vials.

## Insulin (rDNA Origin)

### **Description:**

Insulin is peptide hormone produced in the Islets of Langerhans in the pancreas. The release of this hormone in the human body is most closely tied to blood glucose levels, although a number of other factors including pancreatic and gastrointestinal hormones, amino acids, fatty acids, and ketone bodies are also involved. The main biological role of insulin is to promote the intracellular utilization and storage of amino acids, glucose, and fatty acids, while simultaneously inhibiting the breakdown of glycogen, protein, and fat. It is most notably identified with the control of blood sugar levels, and insulin medications are typically prescribed to people with diabetes, a metabolic disorder characterized by hyperglycemia (high blood sugar). While insulin targets many different organs in the body, this hormone is both anabolic and anti-catabolic to skeletal muscle tissue,<sup>926 927 928</sup> a fact that explains the inclusion of pharmaceutical insulin in the realm of athletics and bodybuilding.

The use of insulin to improve performance and body composition can be a little tricky because this hormone can also promote nutrient storage in fat cells. This, however, is an activity of insulin that can be somewhat managed by the user. Athletes have found that a strict regimen of intense weight training and a diet without excess caloric and fat intake can enable insulin to show a much higher affinity for protein and glucose storage in muscle (as opposed to fatty acid storage in adipose) cells. This is especially true in the post-exercise enhanced-absorptive state, where insulin sensitivity in skeletal muscle has been shown to increase significantly over baseline (rested) levels.<sup>929</sup> When used during the post-training window, the hormone is, likewise, capable of producing rapid and noticeable muscle gains. The muscles often begin to look fuller (and even sometimes more defined) very soon after initiating insulin therapy, and the overall results of therapy are often described as dramatic.

The fact that insulin use cannot be detected by urinalysis has ensured it a place in the drug regimens of many athletes and professional bodybuilders. Note that there has been some progress in drug detection, especially with the analogs, but to date regular insulin is still considered a "safe" drug. Insulin is often used in combination with other "contest safe" drugs like human growth hormone, thyroid medications, and low dose testosterone injections, and together can have a dramatic effect on the user's physique and performance without fear of a positive urinalysis result. Those who do not have to worry about drug testing, however, often find that insulin combined with

anabolic/androgenic steroids can be a very synergistic combination. This is because the two actively support an anabolic state through different mechanisms. Insulin strongly enhances the transport of nutrients into muscle cells and inhibits protein breakdown, and the anabolic steroids (among other things) strongly increase the rate of protein synthesis.

As mentioned, the usual medical purpose for insulin is to treat different forms of diabetes. More specifically, the human body may not be producing enough insulin (Type-I diabetes), or may not recognize insulin well at the cell site although some level is present in the blood (Type-II diabetes). Type-I diabetics are, therefore, required to inject insulin on a regular basis, as they are left without a sufficient level of this hormone. Along with medication, the individual will need to constantly monitor blood glucose levels and regulate their sugar intake. Together with lifestyle modifications such as regular exercise and developing a balanced diet, insulin dependent individuals can live a healthy and full life. When left untreated, however, diabetes can be a fatal disease.

### **History:**

Insulin first became available as a medicine during the 1920s. Credit for the discovery is most appropriately given to Canadian physician Fred Banting and Canadian physiologist Charles Best, who worked together to produce the first insulin preparations, and the world's first effective treatment of diabetes. Their work stemmed from an idea initially proposed by Banting, who as a young doctor theorized that an active extract could be made from animal pancreases to regulate blood sugar in human patients. He needed help to try and actualize his idea, and he sought out world-renowned physiologist J.J.R. Macleod at the University of Toronto. Macleod, initially less than impressed with the unusual concept (but likely impressed with Banting's conviction and tenacity), assigned a couple of graduate students to assist him in his work. A coin flip determined who would work with Banting, and he was eventually paired with graduate student Best. Together they made medical history.

The first insulin preparations they produced were made of crude pancreatic extracts taken from dogs. At one point the supply of laboratory animals was exhausted, and desperate to continue their research, the pair actually began taking stray dogs to supplement their pancreas supply. Shortly after, the two found that they could work with the pancreases of slaughtered cows and pigs, making their work much easier (and ethically acceptable). They successfully treated their first diabetic patient with insulin

in January 1922. By August of that year, they had been successful in treating a group of clinical patients, including 15-year-old Elizabeth Hughes, daughter of former presidential candidate Charles Evans Hughes. Elizabeth was diagnosed with diabetes in 1918, and her dramatic fight for life with the disease gained national attention. Elizabeth would be saved by insulin on the doorstep of starvation, as severe calorie restriction was the only remedy known to slow the disease at the time. Banting and Macleod swiftly won the Nobel Prize for their discovery, which was presented to them approximately a year later in 1923. Shortly after, dispute over credit arose, and ultimately Banting shared his prize with Best, and Macleod shared his prize with J. B. Collip, a chemist that assisted in the extraction and purification process.

After initially declining the assistance in the hopes that they could work out production issues on their own, Banting and his team worked with Eli Lilly & Co. to develop the first mass-produced insulin medicines using their animal extraction techniques. Their production success was extreme and rapid, and the drug became commercially available on a wide scale in 1923, the same year Banting and Macleod won the Nobel prize. That same year, Nordisk Insulinlaboratorium was founded by Danish scientist Augusta Krogh, who desperately wanted to bring back an insulin manufacturing technique to Denmark to treat his wife, who was ill with diabetes. This Denmark firm eventually became Novo Nordisk, the world's second leading producer of insulin next to Eli Lilly & Co.

The early insulin medications were fairly impure by today's standards. They typically contained 40 units of animal insulin per milliliter, in contrast to today's accepted standard concentration of 100 units. The large doses needed with these early low-concentration drugs were not very comfortable for patients, and injection-site reactions were not uncommon. They also contained significant protein impurities that would sometimes cause allergic reactions in users. Despite these faults, the drugs saved the lives of countless individuals who beforehand were faced with a sure death sentence following a diagnosis of diabetes. Eli Lilly and Novo Nordisk improved the purity of their products in the coming years, but no major improvements in insulin technology developed until the mid-1930s, when the first longer-acting insulin preparations began to surface.

The first longer-acting drug made use of protamine and zinc to delay the action of insulin in the body, extending the activity curve and reducing the number of daily injections required for many patients. Dubbed Protamine Zinc Insulin (PZI), the preparation would have an effect lasting as long as 24-36 hours. Neutral Protamine Hagedorn (NPH) Insulin, also known as Isophane insulin,

followed, reaching market by 1950. This preparation was very similar to PZI insulin except that it could be mixed with regular insulin without disturbing the release curve of the respective insulins. In other words, a regular insulin drug could be mixed in the same syringe with NPH insulin, providing a biphasic release pattern characterized by an early peak effect due to the regular insulin, and an extended action brought on by the NPH.

In 1951 the Lente insulins began to surface, which included semilente, lente, and ultra-lente preparations. The amount of zinc used in each varied, producing preparations with distinct and long-acting pharmacokinetics. Unlike previous Insulins, this was also achieved without the use of protamine. Many physicians were soon able to successfully switch their patients from NPH insulin over to a single morning dose of Lente insulin, often heralding the release of the new drugs as a big advance in insulin medications (though some would still require an evening dose with a Lente insulin to maintain full control over blood glucose levels during the 24-hour period). Up to this point the insulin drugs made by the large pharmaceutical companies worked very well. No substantial step forward in the development of new insulin delivery technologies would come for another 23 years.

In 1974, chromatographic purification techniques allowed the manufacture of animal insulin with extremely low impurity levels (less than 1 pmol/l of protein impurities). Novo was the first to release a drug made with this technology, which it called monocomponent (MC) Insulin. Eli Lilly also released a version called "Single Peak" Insulin, likely referring to the single protein peak noticed upon chemical analysis. This advance, though significant, would be short lived. In 1975, Ciba-Geigy produced the first synthetic insulin preparation (CGP 12831). And just three years later, scientists at Genentech were able to produce insulin using modified E. coli bacteria, the first synthetic insulin with an identical amino acid sequence as human insulin (although the animal insulins work fine in humans their structures are slightly different). The U.S. Food and Drug administration approved the first such medicines in 1982, with the acceptance of Humulin R (Regular) and Humulin NPH from Eli Lilly & Co. The name Humulin is a contraction of the words "human" and "insulin"; of course. Novo would follow with semi-synthetic insulins Actrapid HM and Monotard HM.

The FDA has approved a variety of other insulin drug combinations over the years, including various biphasic insulin blends that use differing amounts of rapid and longer-acting insulins. More recently, we have also seen the FDA approval of Eli Lilly's rapid-acting insulin analog Humalog. Several other analogs are also now available

including Lantus and Apidra from Aventis, and Levemir and Novorapid from Novo Nordisk. A number of additional analogs are also under investigation at this time. With the large variety of different insulin medications approved and sold in the U.S. and other nations, it is important to understand that "insulin" represents an extremely broad class of medicines. As a class, these drugs are likely to continue to expand as new agents are developed and successfully tested. Today, it is estimated that 55 million people use some form of injectable insulin on a regular basis to manage their diabetes, making this an extremely important and lucrative area of human medicine.

### **How Supplied:**

Pharmaceutical insulin comes from one of two basic origins, animal or synthetic. With animal source insulin, the hormone is extracted from the pancreas of either pigs or cows (or both) and prepared for medical use. These preparations are further divided into the categories "standard" and "purified," dependent on the level of purity and non-insulin content of the solution. With such products there is always the slight possibility of pancreatic contaminants making their way into the prepared drug. Specifically called biosynthetic, synthetic insulin is produced by a recombinant DNA procedure similar to the process used to manufacture human growth hormone. The result is a polypeptide hormone consisting of one 21-amino acid "A-chain" coupled by two disulfide bonds with one 30-amino acid "B-chain." The biosynthetic process will produce a drug free of the pancreatic protein contaminants possible with animal insulin, and that is structurally and biologically identical to human pancreatic insulin. With the innate (remote) risk of contamination involved with animal insulin, coupled with the fact that the structure is (very slightly) different from human insulin, synthetic human insulin drugs dominate the market today. Biosynthetic human insulin/insulin analogs are also the most common insulins of use among athletes, and the main focus of this profile.

There are a variety of synthetic insulins available, with each possessing unique properties relating to speed of onset, peak and duration of activity, and concentration of dose. This therapeutic variety may allow physicians to tailor a treatment program for insulin-dependant diabetics that allows for the least amount of daily injections and the greatest level of patient comfort. It is important that one should be aware of the individual activity of any insulin drug before attempting its use. Due to the differences between preparations, it is also medically advised that extreme care be taken whenever a physician attempts to switch an insulin-dependant diabetic patient from one form of insulin medication to

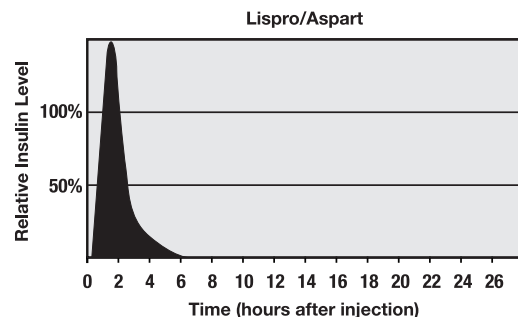
another.

Below is a list showing the distinctions between popular forms of biosynthetic insulin.

### **Short-acting Insulins:**

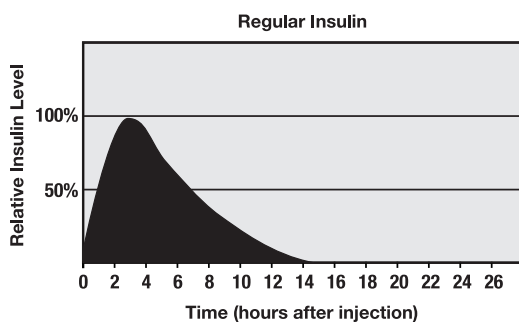
*Humalog® (Insulin Lispro):* Humalog® is a short-acting analog of human insulin, specifically the Lys(B28) Pro(B29) analog of insulin created when the amino acids at positions 28 and 29 are reversed. It is considered equipotent to regular soluble insulin on a unit-to-unit basis, but with more rapid activity.<sup>930</sup> The onset of drug action following subcutaneous administration is approximately 15 minutes, and its peak effect is reached in 30 to 90 minutes. It has a total duration of action between 3 and 5 hours. Insulin lispro is usually used as a supplement to a longer acting insulin product, providing a fast-acting medication that can be taken before or immediately after meals to mimic the body's natural insulin response. Many athletes believe that its short window of effect makes it an ideal insulin medication for physique- or performance-enhancing purposes, as most of its action can be concentrated in the post-training enhanced-nutrient-uptake window.

*Novolog® (Insulin Aspart):* Novolog is a short-acting analog of human insulin created when the amino acid proline at position B28 is replaced with aspartic acid. The onset of drug action following subcutaneous administration is approximately 15 minutes, and its peak effect is reached in 1-3 hours. It has a total duration of action between 3 and 5 hours. Insulin lispro is usually used as a supplement to a longer acting insulin product, providing a fast-acting medication that can be taken before or immediately after meals to mimic the body's natural insulin response. Many athletes believe that its short window of effect makes it an ideal insulin medication for physique- or performance-enhancing purposes, as most of its action can be concentrated in the post-training enhanced-nutrient-uptake window.



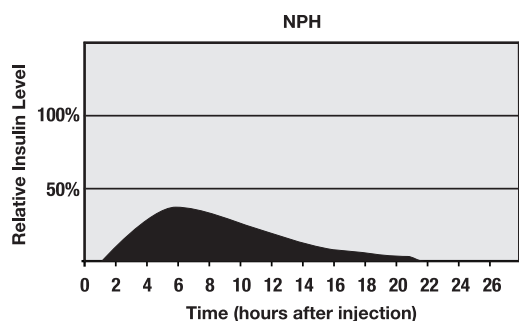
*Humulin®-R "Regular" (insulin Inj):* Identical to human insulin. Also sold as Humulin-S® (Soluble) in some markets, this product consists of zinc-insulin crystals dissolved in clear fluid. There is nothing added to slow the

release of this product, so it is generically referred to as soluble human Insulin. This drug works rapidly and has a short duration of effect. The onset of drug action following subcutaneous administration is 20-30 minutes, and its peak effect is reached in 1-3 hours. It has a total duration of action between 5 and 8 hours. Together with Humalog, these two forms of insulin are the most popular (almost exclusive) choices among athletes and bodybuilders for physique- or performance-enhancement purposes.

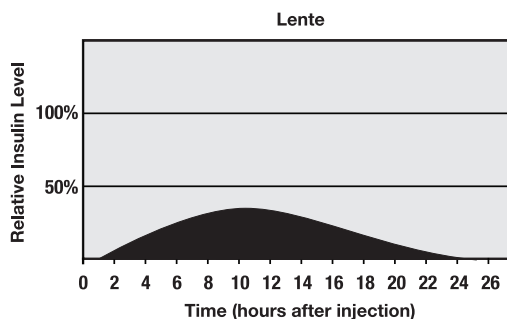


**Intermediate- and Long-acting Insulins:**

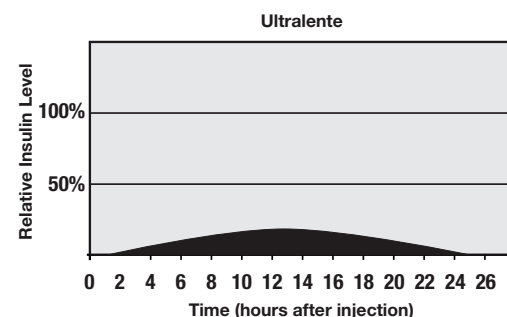
*Humulin®-N, NPH (insulin isophane):* A crystalline suspension of insulin with protamine and zinc to delay its release and extend its action. Insulin isophane is considered intermediate length insulin. The onset of drug action following subcutaneous administration is approximately 1-2 hours, and its peak effect is reached in 4-10 hours. It has a total duration of activity lasting more than 14 hours. This type of insulin is not commonly used for physique- or performance-enhancement purposes.



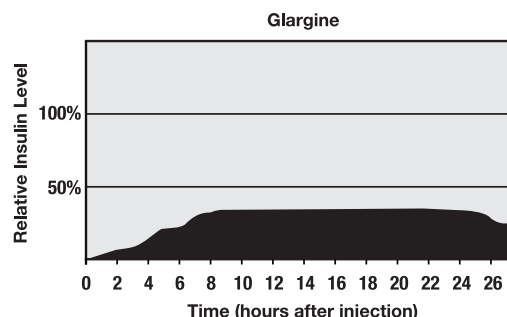
*Humulin®-L, Lente (medium zinc suspension):* A crystalline suspension of insulin with zinc to delay its release and extend its action. Humulin-L is considered an intermediate length insulin. The onset of drug action following subcutaneous administration is approximately 1-3 hours, and its peak effect is reached in 6-14 hours. It has a total duration of activity lasting more than 20 hours. This type of insulin is not commonly used for physique- or performance-enhancement purposes.



*Humulin®-U, Ultralente (prolonged zinc suspension):* A crystalline suspension of insulin with zinc to delay its release and extend its action. Humulin-U is considered a long-acting insulin. The onset of drug action following subcutaneous administration is approximately 6 hours, and its peak effect is reached in 14-18 hours. It has a total duration of activity lasting 18-24 hours. This type of insulin is not commonly used for physique- or performance-enhancement purposes.



*Lantus (insulin glargine):* A long-acting analog of human insulin. Insulin glargine is created when the amino acid asparagine at position A21 is replaced by glycine, and two arginines are added to the C-terminus of the insulin B chain. The onset of drug action following subcutaneous administration is approximately 1-2 hours, and the drug is considered to have no significant peak (it is designed to have a very stable release pattern throughout the duration of activity). Insulin glargine lasts between 20-24 hours in the body following subcutaneous injection. This type of insulin is not commonly used for physique- or performance-enhancement purposes.



**Biphasic Insulins:**

*Humulin® Mixtures:* These are mixtures of regular soluble insulin for a fast onset of action, and a long- or intermediate-acting insulin for a prolonged effect. These are labeled by the mixture percentage, commonly 10/90, 20/80, 30/70, 40/60, and 50/50. Mixtures using Humalog as the rapid-acting insulin are also available.

**Warning: Concentrated Insulin**

The most common forms of insulin come in a concentration of 100 IU of hormone per milliliter. These are identified as "U-100" preparations in the U.S. and many other regions. In addition to this, however, there are also concentrated forms of insulin available for patients that require higher doses and a more economical or comfortable option to U-100 preparations. In the U.S., products containing as much as 5 times the normal concentration, or 500 IU per milliliter, are also sold. These are identified as "U-500" preparations, and are available by prescription only. It can be extremely dangerous or life threatening to replace a U-100 insulin product with a U-500 product without making the necessary dosing adjustments to compensate for the greater drug concentration. Given the general difficulty in accurately measuring athletic doses (2-15 IU) with a drug of such high concentration, U-100 preparations are used almost exclusively for physique- and performance-enhancing purposes.

**Side Effects (Hypoglycemia):**

Hypoglycemia is the primary danger with the use of insulin. This is a dangerous condition that occurs when blood glucose levels fall too low. It is a common and potentially fatal reaction experienced at some time or another by most medical and nonmedical insulin users, so it needs to be taken seriously. It is, therefore, critical to understand the warning signs of hypoglycemia. The following is a list of symptoms that may indicate mild to moderate hypoglycemia: hunger, drowsiness, blurred vision, depressive mood, dizziness, sweating, palpitation, tremor, restlessness, tingling in the hands, feet, lips, or tongue, lightheadedness, inability to concentrate, headache, sleep disturbances, anxiety, slurred speech, irritability, abnormal behavior, unsteady movement, and personality changes. If any of these warning signs should occur, one should immediately consume a food or drink containing simple sugars such as a candy bar or carbohydrate drink. This will hopefully raise blood glucose levels sufficiently enough to ward off mild to moderate hypoglycemia. There is always a possibility of severe hypoglycemia, which is very serious and requires immediate emergency medical attention. Symptoms of this include disorientation, seizure, unconsciousness, and

death. Note that in some cases the symptoms of hypoglycemia are mistaken for drunkenness.

It is also very important to note that you may notice a tendency to get sleepy after injecting insulin. This is an early symptom of hypoglycemia, and a clear sign the user should be consuming more carbohydrates. One should absolutely avoid the temptation to go to sleep at this point, as the insulin may take its peak effect during rest, and blood glucose levels could be left to drop significantly. Unaware of this condition during sleep, the athlete may be at a high risk for going into a state of severe hypoglycemia. The serious dangers of such a state have already been discussed, and unfortunately consuming more carbohydrates during sleep will not be an option. Those experimenting with insulin would, therefore, be wise to always stay awake for the duration of the drug's effect, and also avoid using insulin in the early evening to ensure the drug will not be inadvertently active when retiring for the night. It is also important to make sure others are aware of your use of the drug so that they may inform emergency medical technicians should you lose consciousness or the ability to inform others of your condition due to hypoglycemia. This information can spare valuable (perhaps life saving) time in helping medical professionals establish a diagnosis and provide supportive treatment.

**Side Effects (Lipodystrophy):**

The subcutaneous administration of insulin may cause a localized increase in adipose tissue at the site of injection. This may be compounded by the repeated administration of insulin at the same site of injection.

**Side Effects (Allergy to Insulin):**

In a small percentage of users, the administration of insulin may cause a localized allergy. This may include irritation, swelling, itching, and/or redness at the site of injection. This often subsides as therapy continues. In some instances it may be due to an allergy to an ingredient, or in the case of animal insulin, a protein contaminant. Less common, but potentially more serious, is a systemic allergic reaction to insulin administration. This may include a rash on the whole body, wheezing, shortness of breath, fast pulse, sweating, and/or a reduction in blood pressure. In rare instances this may be life threatening. Any adverse reaction should be reported to a medical authority.

**Administration (General):**

Given that there are varying forms of insulin available for medical use with differing pharmacokinetic patterns, as well as products with different drug concentrations, it is extremely important that the user be familiar with the

dosage and actions of any specific insulin preparation they intend to use so that peak-effect, total time of effect, total dosage, and carbohydrate intake can be closely monitored. Rapid-acting insulin preparations (Novolog, Humalog, and Humulin-R) are the most popular choices for physique- or performance-enhancing purposes, and the subject of the dosing information presented in this book. It is also important to stress that before one considers using insulin they should also become very familiar with using a glucometer. This is a medical device that can give you a quick and accurate reading of your blood glucose level. This device can be indispensable in helping one manage and optimize their insulin/carbohydrate intake.

**Administration (Short-acting Insulin):**

Short acting forms of insulin (Novolog, Humalog, Humulin-R) are designed for subcutaneous injection. Following subcutaneous injection, the injection site should be left alone and not rubbed, to prevent the drug from releasing into circulation too quickly. It is also advised to rotate subcutaneous injection sites regularly to avoid the localized buildup of subcutaneous fat that may develop due to the lipogenic properties of this hormone (see Adverse Reactions: Lipodystrophy). The medical dosage will vary depending on the individual requirements of the patient. Furthermore, changes in such things as diet, activity level, or work/sleep schedule may affect the required insulin dose. Although not recommended medically, it is possible to administer some short-acting insulins via intramuscular injection. This, however, may create more variability (and potential risk) with regard to drug dissipation and hypoglycemic effect.

Insulin dosages can vary slightly among athletes, and are often dependent upon factors like body weight, insulin sensitivity, activity level, diet, and the use of other drugs. Most users choose to administer insulin immediately after a workout, which is the most opportunistic time of the day to use this drug. Among bodybuilders, dosages of regular insulin (Humulin-R) used are usually in the range of 1IU per 15-20 pounds of lean bodyweight; 10IU is perhaps the most common dosage. This amount may be adjusted downward slightly for users of the more rapid-acting Humalog and Novolog preparations, which provide a higher and faster peak effect. First-time cautious users usually ignore bodyweight guidelines, and instead start at a low dosage with the intention of gradually working up to a normal dosage. For example, on the first day of insulin therapy one may begin with a dose as low as 2 IU. Each consecutive post-workout application this dosage might be increased by 1IU, until the user determines a comfortable range. Many feel this is safer and much more tailored to the individual than simply calculating and

injecting a dose, as some find they tolerate slightly more or less insulin than weight guidelines would dictate. Athletes using growth hormone in particular often have slightly higher insulin requirements, as HGH therapy is shown to both lower secretion of, and induce cellular resistance to, insulin.

One must also remember that it is very important to consume carbohydrates for several hours following insulin use. One should generally follow the rule-of-thumb of ingesting at least 10-15 grams of simple carbohydrates per IU of insulin injected (with a minimum immediate intake of 100 grams regardless of dose). This is timed 10 to 30 minutes after subcutaneous injection of Humulin-R, or immediately after using Novolog or Humalog. The use of a carbohydrate replacement drink is often used as a fast carbohydrate source. Properly cautious insulin users will always have a source for simple sugars on-hand in case an unexpected drop in glucose levels is noticed. Many athletes will also take creatine monohydrate with their carbohydrate drink, since the insulin may help force more creatine into the muscles. 30-60 minutes after injecting insulin, one should also eat a good meal and consume a protein shake. The carbohydrate drink and meal/protein shake are absolutely necessary, as without them blood sugar levels may drop dangerously low and the athlete may enter a state of hypoglycemia (see Adverse Reactions: Hypoglycemia). Carbohydrates and proteins are continually provided in sufficient amounts to meet glucose requirements throughout the entire window of insulin effect.

**Administration (Intermediate-acting, Long-acting, and Biphasic Insulins):**

Intermediate-acting, long-acting, and biphasic insulins are designed for subcutaneous injection. Intramuscular injection will cause the drug to be released too rapidly, potentially resulting in hypoglycemia. Following subcutaneous injection, the injection site should be left alone and not rubbed, to prevent the drug from releasing into circulation too quickly. It is also advised to rotate subcutaneous injection sites regularly to avoid the localized buildup of subcutaneous fat due to the lipogenic properties of this hormone (see Adverse Reactions: Lipodystrophy). The medical dosage will vary depending on the individual requirements of the patient. Furthermore, changes in such things as diet, activity level, or work/sleep schedule may affect the required insulin dose. Intermediate-acting, long-acting, and biphasic insulins are not widely used for physique- or performance-enhancing purposes due to their longer acting nature, which makes them poorly suited for concentrating the nutrient partitioning effect of insulin during the short post-workout enhanced-nutrient-uptake

window.

**Availability:**

U-100 insulins may be dispensed from pharmacies in the United States without a prescription. This is so that an insulin-dependent diabetic will have easy access to this life-saving medication. Concentrated (U-500) insulin is sold by prescription only. In most regions of the world, high medical use of the drug leads to easy access and low prices on the black market.

# APPENDIX A: Drug Availability Tables

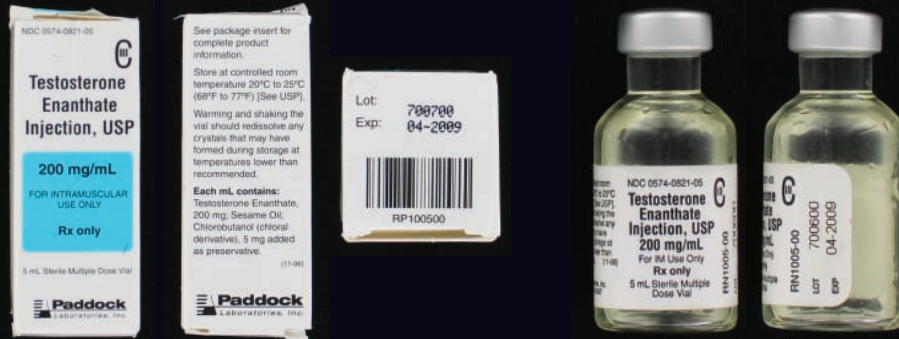
# Listings by Country

<u>Trade Name</u>	<u>Generic Name</u>	<u>Dose</u>	<u>Packaging</u>	<u>Company</u>	<u>Country</u>	<u>Status</u>	<u>Vet</u>
Anabol 10	methandrostenolone	10 mg tablet	500 tablet bottle	British Dispensary	Thailand		
Anabol 15	methandrostenolone	15 mg tablet	100 tablet bottle	British Dispensary	Thailand		
Anabol Tablets	methandrostenolone	5 mg tablet	200, 1000 tablet bottle	British Dispensary	Thailand		
Andriol	testosterone undecanoate	40 mg capsules	10 capsule strip	MSD	Thailand		
Andriolic	oxymetholone	50 mg tablet	100 tablet bottle	British Dispensary	Thailand		
Azolol Plus	stanazolol	2.5, 5 mg tablet	400 tablet bottle	British Dispensary	Thailand		
Bonavar	oxandrolone	2 mg tablet	n/a	British Dispensary	Thailand		
Cetabon	oxandrolone	2.5 mg tablet	50 tablet box	Meredian	Thailand		
Cybiolic	stanazolol (oral)	2 mg tablet	10 tablet strip	Great Eastern	Thailand		
Cyponax	testosterone cypionate	200 mg/ml	10 ml vial	Asia Pharma	Thailand		
Danabol DS	testosterone cypionate	100 mg/ml	2 ml ampule	T.P. Drug Laboratories	Thailand		
Deca-Durabolin®	methandrostenolone	10 mg tablet	500 tablet bottle	March	Thailand		
Decabolic	nandrolone decanoate	25, 50 mg/ml	1 ml ampule	MSD	Thailand		
Depo-Test 250	nandrolone decanoate	200 mg/ml	10 ml vial	Asia Pharma	Thailand		
Diabol-10	testosterone enanthate	250 mg/ml	10 ml vial	Unigen	Thailand		
Dronabol	methandrostenolone	10 mg tablet	500 tablet bottle	Bukalo Trading Co.	Thailand		
Durabolic	methandrostenolone	5 mg, 10 mg tablet	n/a	Bangkok Lab	Thailand		
Enantibolic	nandrolone phenylpropionate	10 mg tablet	500, 1000 tablet bottle	Berich	Thailand		
Halofestin®	testosterone enanthate	100 mg/ml	10 ml vial	Asia Pharma	Thailand		
Melic	fluoxymesterone	250 mg/ml	10 ml vial	Asia Pharma	Thailand		
Metesto	methyltestosterone	5 mg tablet	100 tablet bottle	Pharmacia	Thailand		
Meihandon	nandrolone phenylpropionate	5 mg tablet	1000 tablet bottle	Pharmacia	Thailand		
Methyltestosterone	methyltestosterone	10 mg capsule	1000 tablet bottle	Pharmasant	Thailand		
Nandro 250	nandrolone decanoate	25 mg tablet	1000 tablet box, bottle	Acdhon	Thailand		
Nebido	testosterone undecanoate (inj)	5 mg tablet	1000 tablet bottle	Acdhon Co.	Thailand		
Norabon	nandrolone phenylpropionate	10 mg capsule	20, 100, 500, 1000 capsules	March	Thailand		
Oxyanabolic	oxymetholone	250 mg/ml	10 ml vial	Unigen	Thailand		
Propiobolic	testosterone propionate	25 mg/ml	4 ml ampule	Bayer	Thailand		
Provironum	mesterolone	25 mg/ml	1 ml ampule	Phihalab	Thailand		
Stanabolic	stanazolol (oral)	50 mg/ml	100 tablet box	Asia Pharma	Thailand		
Stanabolic	stanazolol (oral)	100 mg/ml	10 ml vial	Asia Pharma	Thailand		
Stanabolic	stanazolol (oral)	25 mg tablet	150 tablet box	Bayer	Thailand		
Stanabolic	stanazolol	10 mg tablet	100 tablet box	Asia Pharma	Thailand		
Stanazolodon	stanazolol (oral)	50 mg/ml	10 ml vial	Asia Pharma	Thailand		
Stanazolol	stanazolol (oral)	2 mg tablet	1000 tablet bottle	Acdhon Co.	Thailand		
Stanztab	stanazolol (oral)	5 mg tablet	200 tablet bottle	March	Thailand		
Sustabolic	stanazolol (oral)	10 mg tablet	100 tablet box	Unigen	Thailand		
Sustanon 250®	Sustanon 250 (testosterone blend)	250 mg/ml	10 ml vial	Asia Pharma	Thailand		
Sustanon 250	Sustanon 250 (testosterone blend)	250 mg/ml	10 ml vial	MSD	Thailand		
Test Comp 250	Sustanon 250 (testosterone blend)	250 mg/ml	1 ml ampule	MSD	Thailand		
Testolic	testosterone propionate	50 mg/ml	10 ml vial	Unigen	Thailand		
Testosterone Propionatej	testosterone propionate	250 mg/ml	2 ml ampule	T.P. Drug Laboratories	Thailand		
Testoviron®-Depot	testosterone propionate	25 mg/ml	1 ml ampule	March	Thailand		
TP Men Hormone	testosterone enanthate	250 mg/ml	1 ml ampule	Bayer	Thailand		
Viormone	methyltestosterone	10 mg dragee	24 tablets	TP Drugs	Thailand		
Andriol	testosterone propionate	50, 100 mg/ml	1 ml ampule	Paines	Thailand		
	testosterone undecanoate	40 mg capsules	n/a	MSD	Tunisia		

# Testosterone Enanthate



Enanthate generic from Paddock (U.S.)



Previous packaging for Paddock generic (U.S.)

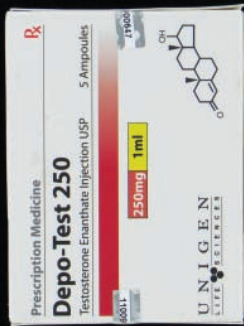


Enanthate generic from Watson (U.S.)

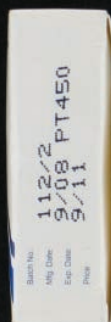


10mL version from Watson (U.S.)

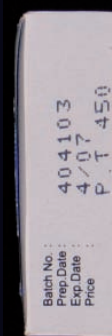
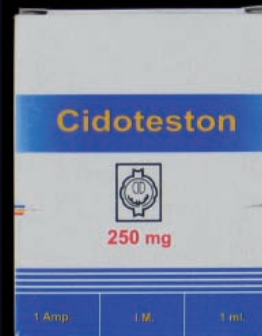
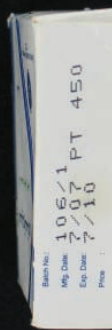
U.S. Delatestryl from Savient



Depo-Test 250 ampules and vial from Unigen (Thailand)

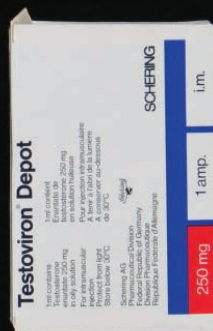
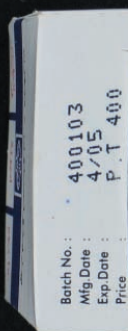


Cidoteston from CID (Egypt)



Counterfeit Egyptian Cidoteston

Older box from CID



Primoteston-Depot from CID/Schering Egypt (NLM)

Testoviron Depot from Lebanon



Winstrol tablets from Desma (Spain)



Winstrol Depot from Desma (Spain)



Counterfeit Desma box/ampules      Counterfeit on left      Zambon Winstrol tablets (Spain) NLM



Winstrol Depot from Zambon (Spain) NLM      Counterfeit Zambon vial

**Growth Hormone**

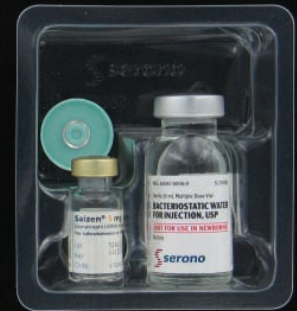


U.S. Serostim



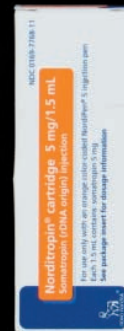
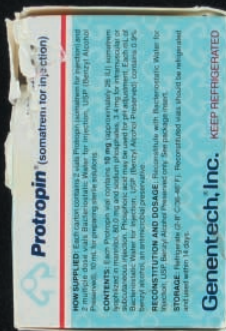
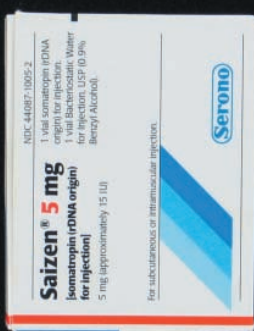
Humatrope (U.S.)

Genotropin (U.S.)



Older U.S. Serostim box

U.S. Saizen



Old U.S. Saizen packaging

U.S. Protropin (somatrem)

(U.S.)

Signature (U.S.) NLM