ANABOLIC STEROIDS
A QUESTION OF MUSCLE

Human Experimentation in Anabolic Steroid Research

MICHAEL SCALLY, M.D.

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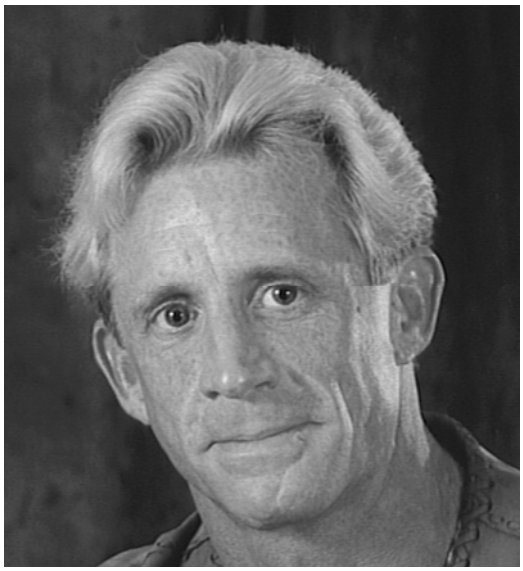
ABOUT THE AUTHOR



Dr. Scally's education includes a double degree major in Chemistry (1975) and Life Sciences (1975) from the Massachusetts Institute of Technology (M.I.T.) Cambridge, MA. Following, from 1975-1980, in the M.I.T. Division of Brain Sciences & Neuroendocrinology Dr. Scally researched and published investigations on neurotransmitter relationships. Dr. Scally's research included involvement and participation in the earliest studies detailing the role of tryptophan, serotonin, and depression. During this time, he entered the prestigious Health Sciences & Technology Program, a collaboration of M.I.T. and Harvard Medical School. In June 1980, Dr. Scally was awarded by Harvard Medical School a Doctorate of Medicine, M.D. Continuing his education, Dr. Scally trained at Parkland Memorial Hospital, Southwestern Medical School. Scally completed the first year of postgraduate medical residency in general surgery followed by postgraduate medical residency in anesthesiology.

In private practice, Scally served as Chief of Anesthesia at Sam Houston Memorial Hospital, Houston, Texas (1983-1992), West Houston Surgical Center, Houston, Texas (1984-1994), and Brazosport Memorial Hospital, Lake Jackson, Texas (1990-1992). Dr. Scally was responsible for the creation and implementation for Sam Houston Memorial Hospital's first cardiothoracic and neurological surgery unit. During this same time, in 1982, Dr. Scally was the first physician to design, operate, and mange an outpatient surgery facility, West Houston Surgical Center, in Houston, Texas. In 2007, more than twenty-five years later, outpatient surgery has become commonplace. Brazosport Memorial Hospital sought out Dr. Scally's leadership role in writing and implementing procedure and policy for the important accreditation by the Joint Commission on Accreditation of Hospitals.

Anesthesiologist Dr. Scally from his experience, education, and historical events became uniquely qualified to approach a medical problem with increasing concerns for the public health and welfare. The focus of Dr. Scally's entry into direct patient care practice was on preventative and general healthcare, with areas of particular specialization on the adverse effects of

supplements and medications. His professional memberships include The Endocrine Society and the American Association of Clinical Endocrinologists (AACE).

In 1995, Dr. Scally inquired to Wyeth Pharmaceuticals about the association between primary pulmonary hypertension and pondimin (fenfluramine). The inquiry focused on the request for studies demonstrating this very serious adverse effect from pondimin use. Significantly, this inquiry later was evidence in the class action suit against Wyeth and instrumental in showing that the known adverse effects were known to Wyeth but not revealed to the public.

Within a short time later, Dr. Scally discovered an OTC supplement containing an ingredient toxic to the thyroid. Further investigation by Scally revealed the presence of a drug, titriacol, present within OTC supplements (www.cfsan.fda.gov/~lrd/tptriax.html). The reporting of this to the federal agency, MedWatch, was instrumental in the national seizure of the supplement thus avoiding a disaster to the public health and welfare.

The medical community holds that the hypogonadism does not occur after stopping prescription androgens and is not a medical concern. The accepted standard of care within the medical community is to do nothing. This is proving to not be the case and now jeopardizes the health and welfare of countless individuals. Dr. Scally's research and investigations early on recognized the lack treatment for individuals using androgens after their cessation, both licit and illicit. Dr. Scally has personally cared for thousands of individuals using androgens. His concerns and treatments for the period after androgen cessation has been presented before the Endocrine Society, American Association of Clinical Endocrinologists, American College of Sports Medicine, and the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, as well as the focus of now published peer-reviewed literature.

Consistent with the AMA Code of Ethics, Scally discussed and published his findings in peer reviewed medical literature. The AMA code of ethics on new medical procedures states that physicians have an obligation to share their knowledge and skills and to report the results of clinical and laboratory research. The prompt presentation before scientific organizations and timely publication of clinical and laboratory research in scientific journals are essential elements in the foundation of good medical care. This tradition enhances patient care, leads to the early evaluation of new technologies, and permits the rapid dissemination of improved techniques.

In this book, Dr. Scally exposes the ethical, legal, and medical violations in androgen research. After reading the book, one is awestruck that medical research continues that violates the most basic and fundamental human rights. That this is possible is easily due to pharmaceutical industry funding, governmental ignorance, and medical community complicity. Dr. Scally maintains a website on androgen use, including administration and cessation, located at http://www.asih.net.

CHALLENGE

A challenge for the physician investigator willing to expose the use of unsound scientific design and methodology of many powerful, but disillusioned, researchers cited within the studies of this book is an unheralded opportunity. It will not be possible, read impossible, to repeat the findings of the studies that include the period after anabolic androgenic steroid cessation, hypogonadism, with the end-point being the study groups return to their baseline values. The studies within the book completely and entirely dismiss and ignore the significance of sex hormone measurements. Further, they ignore a basic tenet of life's characteristics, homeostasis.

CONTENTS

PREFACE

"The discovery of truth is prevented more effectively, not by the false appearance things present and which mislead into error, not directly by weakness of the reasoning powers, but by preconceived opinion, by prejudice." Arthur Schopenhauer (1788–1860), German philosopher.

"All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident." Schopenhauer.

ANABOLIC STEROIDS: A QUESTION OF MUSCLE - PROBLEMS & SOLUTIONS is a chronicle of current day human research abuses. Clinical application of published study results is dependent upon sound research design. Anabolic-androgenic steroid (AAS) research focuses only on the period of AAS administration while dismissing and ignoring the period after AAS cessation that directly affect the validity of their conclusions, adverse body composition changes. The research design of these studies does not take into consideration that AAS use causes a disruption of the hypothalamic-pituitary-testicular axis, resulting in a state of anabolic steroid induced hypogonadism (ASIH) that after AAS cessation continues for an unknown duration and severity. Critically, the period of hypogonadism exposes the subjects to the known adverse risks of hypogonadism. Significantly, the problem of anabolic-androgen steroid induced hypogonadism presents an opportunity. Solutions to this disorder are important and are found within the book.

The anabolic androgenic steroid research present within the book conclude that anabolic steroid administration results in increases in muscle mass and muscle strength in many chronic diseases where there is an associated loss of muscle mass and muscle strength. Based on these conclusions, the physician-investigators recommend their use as a possible means of decreasing morbidity and mortality. However, these studies fail to consider the period after anabolic steroid cessation, a period where there is loss of the muscle mass and muscle strength gains during anabolic steroid administration. In one-hundred percent of the published studies, a period of hypogonadism ensues after anabolic steroid cessation. Despite the published literature findings, these studies do not include this period after anabolic steroid cessation, a period that if included would have negate effects and probably eliminate their study conclusions.

Most horrific and disturbing is these individuals with chronic diseases will now have exposure to a comorbid condition, hypogonadism, which will adversely affect their public health and welfare. Moreover, the medical community has steadfastly refused to recognize the peer-reviewed literature on anabolic-androgenic steroids, holding that hypogonadism after stopping prescription anabolic-androgenic steroids is of no medical consequence.

The ridiculous and bizarre nature with which these beliefs are so firmly held in the face of absent scientific literature and overwhelming scientific literature to the contrary is beyond description. However, they are telling for the ignorance and indicate misconduct that runs much deeper within the scientific community. This is plain and clear by a recent OHRP response written from a position of no, none, support from published literature (Appendix E OHRP Response):

> "Your letters indicate that you are deeply concerned about the adverse health consequences associated with the cessation of the use of prescribed AAS and particularly with the development of hypogonadism. You assert that these investigators and institutions did not warn or protect research subjects from the risk of hypogonadism associated with the cessation of therapeutic doses of AAS."
>
> "The HHS protection of human subjects regulations are designed, in part, to protect research subjects from and inform them about known risks that they may incur while participating in a research study. From OHRP's examination of this issue, we have found that the mainstream medical community currently does not recognize that hypogonadism results from the cessation of FDA approved doses of therapeutic AAS. Therefore, it would be reasonable for an institutional review board (IRB) not to attempt to minimize the risk of developing hypogonadism after ceasing the use of therapeutic AAS, and to approve an informed consent process that does not address the development of hypogonadism as a risk of the research, because this risk is not recognized by the mainstream medical community."

Be afraid. Be very afraid. OHRP is a government agency mandated to protect the public from human research abuse. The basis for OHRP action is supposed to be on sound scientific principles and evidence, yet as the above tells the agency uses fiction, fables, and story as their foundation. This from an agency meant to protect, Office Human Research Protection, within its title. Be afraid. Be very afraid.

The beat cop, "gumshoe," observes and reports. In response, preventive action averts disaster and tragedy while ignorance and dismissal invites doom and gloom. To catch a perpetrator, the crime scene investigator finds the evidence and follows the science. With a serial offender, locate and recognize the pattern. With these in hand, the suspect confesses or lies. Lies, being duplicitous expose themselves and attempts at doublethink fail. Their only recourse: deny, deny, deny.

Uncovering the nature of human research abuse follows a similar pattern. The clinical practitioner caring for individual patients on a daily basis must observe, examine, and report. After tens, hundreds, thousands of patients all with the same or similar complaints, physical findings, and laboratory studies there is little doubt to the diagnosis. In medicine, reporting to the

appropriate authorities includes the medical community at-large (presentations and publications) and government agencies (FDA and OHRP). Whether there is prevention of disaster and tragedy depends upon the medical community and governmental agency response. Unfortunately, in the current era and the past, this proves to be inadequate and action takes place upon the occurrence of tragic events. In the rare circumstance, the persistence and perseverance of lone individuals may help avoid the inevitable.

The lies — obfuscation, misdirection, contradiction — present within the pages of this book in support of abuses in human anabolic steroid research place the health and welfare of thousands of individuals in jeopardy. Feigned ignorance of physician-investigators and government officials only furthers and perpetuates this ongoing harm.

Chapter 1 provides a background on testosterone and related analogues, anabolic steroids. Chapter 2, hypothalamic pituitary testicular axis, describes the homeostatic mechanisms in the control and regulation of testosterone levels. A disruption of homeostasis results in disease, specifically hypogonadism, including anabolic steroid induced hypogonadism (ASIH), Chapter 3. Chapter 4, Henry K. Beecher: Echoes & Reverberations, forty plus years later since publication of Beecher's report on ethical research abuses, one might expect that ethical violations would be rare, that physician-researchers would adhere to the highest of ethical standards, the Nuremberg Code principles would be the commonplace guidepost, and an individual's health and welfare is of the utmost priority. Sadly, the polar opposite is the case. Vulnerable populations exposed to AAS administration with no consideration for the period after AAS cessation include human immunodeficiency virus (HIV), Chapter 5; chronic obstructive pulmonary disease (COPD), Chapter 6; chronic kidney disease: hemodialysis, Chapter 7; osteoporosis & glucocorticoids, Chapter 8, and sarcopenia, Chapter 9. Chapter 10 reveals the governmental ignorance, institutional complicity, and investigator doublethink in defense of unsound research design, unsound research methodology, and improper informed consent. Chapter 11 describes possible solutions to the medical problem anabolic steroid induced hypogonadism (ASIH).

CHAPTER 1 - TESTOSTERONE & ANABOLIC STEROIDS

Testosterone is the primary male sex hormone and is necessary for the maintenance of both androgenic and anabolic effects. Androgenic effects produce or stimulate the development of secondary male characteristics (masculinization) and reproduction (spermatogenesis). Anabolic effects promote or stimulate the building of tissue (bone and muscle). Serum testosterone level has a positive correlation with protein synthesis that results in muscle tissue development, muscular strength, bone density, sexual desire (libido), erythropoiesis, mental cognition, and verbal fluency. Anabolic Steroids (AAS) are a class of compounds that include any drug or hormonal substance, chemically and pharmacologically related to testosterone that stimulates the growth or manufacturing of body tissues (bone and muscle). This includes testosterone, testosterone undecanoate, testosterone cypionate, testosterone enanthate, oxandrolone, oxymetholone, nandrolone decanoate, and stanazolol.

CHAPTER 2 - HYPOTHALAMIC PITUITARY TESTICULAR AXIS

The hypothalamic pituitary testicular axis (HPTA) is the homeostatic system responsible for maintaining, supporting, and ensuring reproduction, bone density, muscle mass, and other important and vital physiological and psychological processes. Homeostasis is the process by which an organism maintains constant internal conditions in the face of a varying external environment. The testicular production of testosterone and spermatozoa is dependent upon stimulation by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from the pituitary, respectively. Absent LH and FSH, there is no testicular testosterone production or spermatogenesis, respectively. Testosterone along with other factors, in turn, inhibits pituitary LH and FSH production and secretion, thereby, establishing a negative feedback loop.

CHAPTER 3 - HYPOGONADISM & ANABOLIC STEROID INDUCED HYPOGONADISM (AIH)

Hypogonadism is a disturbance of HPTA homeostasis. Hypogonadism is inadequate gonadal function, as manifested by deficiencies in spermatogenesis and/or the secretion of testosterone. Other than infertility, laboratory studies are the gateway to a proper diagnosis. Testosterone is the initial screening laboratory study. Gonadotropins, LH and FSH, classify the disorder. A decrease in serum testosterone combined with a normal or decreased gonadotropin, LH and FSH, classifies the disorder as hypogonadotropic, secondary, or central hypogonadism.

Anabolic steroid induced hypogonadism (ASIH) is the functional incompetence of the testes with subnormal or impaired production of testosterone or spermatozoa due to administration of anabolic steroids, including testosterone. ASIH occurs in one-hundred percent of individuals upon AAS cessation. The only variable is the duration and severity of ASIH. Declining, or suppressed, circulating testosterone levels because of either pathophysiological or induced hypogonadal conditions can have many negative consequences in males. Declining levels of testosterone cause a progressive decrease in muscle mass, decrease in muscular strength, increased body fat, loss of libido, bone loss, and mood disturbances including depression.

CHAPTER 4 - HENRY K. BEECHER: ECHOES & REVERBERATIONS

In 1966, anesthesiologist Dr. Henry K. Beecher wrote in the New England Journal of Medicine, "Ethics and Clinical Research," describing 22 examples of research studies with controversial ethics that had been conducted by reputable researchers and published in major journals. Beecher provides estimates and concludes, "[u]nethical or questionably ethical procedures are not uncommon." Henry K. Beecher's publication in 1966 covers many areas of medicine while this book restricts itself to AAS research. The number of human research subjects affected alone by unethical and unsound practices in AAS research numbers into the thousands. Those similarly affected by physicians that have implemented these course of treatments in their own patients assuredly numbers in the hundreds of thousands.

CHAPTER 5 - HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Published studies of growth hormone and anabolic steroid treatments of wasting syndrome have not included prolonged follow-up and survival information. There are no studies

finding improved survival associated with hormone-based treatments of wasting syndrome. To date, prescription of anabolic steroids or growth hormone is not associated with improved survival. In addition, the studies in the published literature do not account for anabolic steroid induced hypogonadism (ASIH). Barring medical intervention to minimize or prevent ASIH after AAS cessation, there is no empirical evidence for the use of AAS treatment to produce positive body composition changes, and the use of anabolic steroids to promote positive body composition changes is not justified, dangerous, and abuse. Yet, as the following illustrates these studies populate the peer-reviewed literature.

CHAPTER 6 - CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) is primarily a disease of the elderly thus placing those affected at a higher risk of morbidity and mortality. Any additional comorbid disease will undoubtedly lead to additional adverse outcomes, not less. In already compromised individuals, hypogonadism, whether or not induced, is a disease with associated particularly significant adverse events that is clearly such a comorbid condition. There can be no plausible reason or justification, none, to expose COPD individuals to AAS treatment without consideration for the period of hypogonadism after AAS cessation. Yet, a number of published studies utilizing AAS treatment completely ignore this period that not only endangers the subjects but also additionally affects adversely the results and conclusions of the studies. The basis for AAS treatment of COPD individuals is tenuous at best and at worst an enterprise of conflicted physicians looking for academic and financial rewards.

CHAPTER 7 - CHRONIC KIDNEY DISEASE: HEMODIALYSIS

In 1989, a clinical study using AAS for uremic anemia in male chronic renal failure (hemodialysis) patients, both reported and warned of the period of hypogonadism after AAS cessation. Twenty-three patients who received anabolic steroids showed significantly lower testosterone values than did patients without these steroids. The authors warned that anabolic steroid administration is a possible cause for uremic hypogonadism. Thus, care is important when prescribing these analogues. The adverse effects of AAS demonstrated in these early studies went completely ignored in later studies on identical populations, hemodialysis patients.

CHAPTER 8 - OSTEOPOROSIS & GLUCOCORTICOIDS

Osteoporosis is bone loss. Glucocorticoids are the most commonly prescribed drug for many conditions. Glucocorticoid adverse effects include muscle loss and bone loss. A major health complication of the elderly is the increased risk of falls and fractures. Injury and mortality due to fractures and falls can be attributed to the loss in lean muscle, functional strength, bone loss, balance, or a combination of these variables. Androgen replacement therapy in hypogonadal men as well as pharmacological androgen therapy in eugonadal men increases muscle mass and strength. Based upon this premise, published studies have reported on the effects of AAS treatment in opposing some of the catabolic glucocorticoid effects on muscle and bone. These studies, in chronically ill individuals, fail to account for the period after AAS cessation.

CHAPTER 9 - SARCOPENIA

Sarcopenia is the progressive, age-related decline in muscle mass and strength. Published literature includes the use of anabolic steroids to improve measures of body composition in sarcopenia. Published studies on the oral anabolic steroids oxymetholone, oxandrolone, and testosterone undecanoate draw conclusions that treatment produces positive anabolic, body composition, changes that might be beneficial for the age related loss of muscle mass and strength. Numerous studies publish the results of the positive anabolic improvements in body composition disregarding the period after AAS cessation. ASIH will negate the positive body composition benefits but impose upon the patient the additional signs and symptoms of hypogonadism. With no guarantee for HPTA normalization and no consideration of caring physicians for ASIH, the patient is in a state of health worse than prior to AAS administration.

CHAPTER 10 – DOUBLETHINK

Doublethink is an integral concept in George Orwell's dystopian novel Nineteen Eighty-Four, and is the act of holding two contradictory beliefs simultaneously, fervently believing both. On June 16, 2003, a complaint filed with the Office for Human Research Protections (OHRP), listed a series of allegations for violations of 45 C.F.R. 46, Subpart A, Protection of Human Subjects, in a published study funded by public sources (Schroeder ET, Singh A, Bhasin S, et al. Effects of an oral androgen on muscle and metabolism in older, community-dwelling men. Am J Physiol Endocrinol Metab 2003;284:E120-8). The response includes fabrications and falsifications of published literature in order to defend the indefensible. It does not require an in-depth review to notice the contradictions outlined in the USC and CDU responses. This is inexcusable from a group of researchers assumed to be among the best in their respective fields. The details of the responses transcend reality and transport one to the Orwellian world of doublethink.

CHAPTER 11 – SOLUTIONS

The problems of anabolic steroid research present a unique and valuable opportunity. The solution to the problem of androgen induced hypogonadism makes available treatments for the adverse psychological effects of anabolic steroid cessation, both prescription and nonprescription, previously incorrectly attributed to dependency or addiction, combinatorial therapy with androgens for wasting conditions without the attendant hypogonadism, combinatorial therapy with androgens for obesity, and mitigation of future post male contraceptive infertility.

Anabolic androgenic steroid research focuses only on the period of AAS administration, while at the same time purposely dismissing and ignoring the period after AAS cessation that affect the validity of their conclusions. These same pundits that steadfastly or stubbornly refused to study and believe the association between anabolic steroids and muscle, now in a similar manner steadfastly or stubbornly refuse to study the period after anabolic androgenic steroid cessation to the detriment of the public health and welfare.

It is time for the medical community to act responsibly, intelligently, and forcefully and take control of the medical care for individuals. At the very minimum the following studies are needed immediately: (1) investigations on an accurate estimate of ASIH prevalence, (2) dose-

response study on AAS and HPTA normalization that are inclusive for AAS (type, dose, & duration), signs, and symptoms (similar and identical to those done with GnRH induced hypogonadism), (3) clinical investigations on medical treatments (prevent, eliminate, or minimize) for ASIH, (4) investigations on the development of protocols or programs to effect positive body composition changes without the attendant consequences of ASIH, and (5) collaborative clinical investigations regarding dependence, abuse, and addiction of androgens in relation to ASIH.

- 1 -

TESTOSTERONE & ANABOLIC STEROIDS

Testosterone is the primary male sex hormone and is necessary for the maintenance of both androgenic and anabolic effects. Androgenic effects produce or stimulate the development of secondary male characteristics (masculinization) and reproduction (spermatogenesis). Anabolic effects promote or stimulate the building of tissue (bone and muscle). Serum testosterone level has a positive correlation with protein synthesis that results in increases in muscle tissue development, muscular strength, bone density, sexual desire (libido), erythropoiesis, mental cognition, and verbal fluency. Anabolic Steroids (AAS) are a class of compounds that include any drug or hormonal substance, chemically and pharmacologically related to testosterone that stimulates the growth or manufacturing of body tissues (bone and muscle). This includes testosterone, testosterone undecanoate, testosterone cypionate, testosterone enanthate, nandrolone decanoate, oxandrolone, and oxymetholone.

Humans have known since ancient times that "...you can take away the vigor of men by removing their testes." Many cannibal tribes practiced castration on their victims several weeks prior to the sacrificial ritual. Ancient Hindus, Romans, and Egyptians advocated the use of the testicles of wild animals as treatment of impotence. The testicular transplantation experiments of Hunter and Berthold established that the secretions of the testis could regulate the growth of capon and male behavior, remote from the site of production. The discovery of testosterone linked to medical purposes took place in the 18th Century when the Scottish physician John Hunter (1728-1793) developed methods for testicular transplantation experiments.

In 1849, the German Professor Berthold of Göttingen discovered that the castration-induced decline in sexual behavior and atrophy of the combs in roosters were restored when testicular tissue was implanted into the abdominal cavity.[1] In June 1889, the French physiologist Charles Édouard Brown–Séquard announced at the Société de Biologie in Paris that he had devised an excellent therapy for his body and mind. He injected himself liquid extracts from the testicles of dogs and guinea pigs that increased his physical strength and intellectual energy, relived his constipation, and lengthened the arc of his urine.[2]

In 1931, Butenandt presented the first report on the isolation of a substance with androgenic activity.[3] The compound androsterone was isolated in an amount of 15 mg from 15000 liter of male urine. In 1935, Dutch researchers isolated a small amount of substance, coined testosterone, from nearly 100 kg of bull testicles.[4] Consequently, scientists drew the

conclusion that the testicles must contain something more potent than did urine. Due to the structural similarity between the hormones (androsterone) found in urine and testosterone, Butenandt and Hanisch assumed that testosterone must be metabolized in the body.[5]

Later the same year, in 1935, two major independent research teams contributed to the successful identification of the primary male hormone testosterone.[6] For this discovery and the chemical synthesis of testosterone from cholesterol, Butenandt and Ruzicka were awarded the Nobel Prize for Chemistry in 1939. It was later discovered that the testosterone molecule has the potential to be oxidized or reduced to approximately 600 related steroids. They were given the name androgens, which derives from the Latin words andros (man) and gennan (to produce).[7]

The synthesis of testosterone in men occurs primarily in the Leydig cells of the testes, with a small percentage produced in the adrenal cortex.[8] The testes are the source of more than 95% of the circulating testosterone in men, although the adrenal cortex produces large amounts of the testosterone precursor steroids dehydroepiandrosterone (DHEA) and androstenedione. Testosterone synthesis, the primary androgenic hormone, is through a series of enzymatic reactions that convert cholesterol to testosterone. The Sertoli cells of the testes are responsible for the production of sperm.

The usual normal range for testosterone levels in serum samples is 300–1000 ng/dL (10–35 nM/L).[9] Estimate of the blood production rate of testosterone in normal adult men ranges from 5.0-7.5 mg/day.[10] The testosterone content of the adult human testis is only about 50 μg (1 μg/g testis), indicating that nearly all of the synthesized testosterone is released into the circulation.

There is also a diurnal variation in circulating testosterone levels in adult men, with highest levels in the early morning, followed by a progressive fall throughout the day, to nadir levels in the evening and during the first few hours of sleep.[11] Frequent sampling of peripheral blood in adult men reveals small moment-to-moment fluctuations in total testosterone of 10-15%. Nadir values are approximately 15% lower than morning values, although differences of as much as 50% can occur.[12] Because pulse frequency is rapid and pulse amplitude is relatively low, only small fluctuations are generally observed in peripheral blood. Therefore, a single blood sample is an adequate assessment of testosterone production on a given day.[13]

Total blood testosterone is comprised of both bound and unbound testosterone. Testosterone circulates in a free or unbound state, bound to sex hormone binding globulin (SHBG), or bound to the blood protein albumin. Free testosterone is testosterone that is unbound, does not include albumin or SHBG bound testosterone. Bioavailable, non-SHBG, testosterone includes free testosterone and testosterone that is bound to albumin but does not include sex hormone binding globulin-bound testosterone. Of the total testosterone in the plasma of adult men, about 45% is bound with high affinity to sex hormone-binding globulin (SHBG), 50% is loosely bound to albumin, 1-2% to cortisol-binding globulin, and less than 4% is free (not protein bound).[14]

Several laboratory assays and methods of calculation are used to measure testosterone: total testosterone (T = protein bound + free), free testosterone (FT = not bound to proteins), and

bioavailable testosterone (BT = free + albumin bound). The methods used to conduct the measurements vary in their accuracy, standardization, the extent of validation, and the reproducibility of results. Radioimmunoassay measurement of total testosterone is a validated, standardized, and reproducible assay.[15] Commercial assay kits using unextracted serum or plasma and a ^{125}I-labeled testosterone tracer with solid phase separation methods are technically easy to use, precise, relatively inexpensive, and sufficiently accurate for most purposes.[16]

In radioimmunoassay (RIA), a fixed concentration of labeled tracer antigen, testosterone, is incubated with a constant amount of antiserum such that the concentration of antigen binding sites on the antibody is limiting, for example, only 50% of the total tracer concentration may be bound by antibody.[17] If unlabeled antigen, serum testosterone, is added to this system, there is competition between labeled tracer and unlabeled antigen for the limited and constant number of binding sites on the antibody, and thus the amount of tracer bound to antibody will decrease as the concentration of unlabeled antigen increases. This can be measured after separating antibody-bound from free tracer and counting the bound fraction, the free fraction, or both. A calibration or standard curve is set up with increasing amounts of known antigen, and from this curve, the amount of antigen in the unknown samples can be calculated. Thus, the four components for a radioimmunoassay system are an antiserum to the compound to be measured, the availability of a radioactively labeled form of the compound, a method whereby antibody-bound tracer can be separated from unbound tracer, and a standard unlabeled material.

Specificity is one of the most important requirements of immunoassays. Interference occurs in all situations in which the antibody is not specific for the analyte. Consequently, assessment of specificity is a vital step in the optimization of every new immunoassay. Poor specificity results in interference from compounds of similar molecular structure or which carry similar immunoreactive epitopes. An epitope is a localized region on the surface of an antigen that is capable of eliciting an immune response and of combining with a specific antibody to counter that response.

In determining the overall specificity of an assay, a major factor is the cross-reactivity of the antibody. The extent to which cross-reacting substances affect an assay depends on a number of factors: their concentration relative to the analyte, their relative antibody-binding affinities, and the assay design. However, other steps such as preanalytical purification (e.g. extraction and/or chromatography) can be used to eliminate unwanted interference and improve assay specificity. Cross-reaction is the binding or interference in the binding of the antibody by some agent other than the compound chosen to be measured. Specification sheets accompanying antibody shipments usually supply known cross reactivity information in table form for other materials typically present in the measured sample material that may cross-react with the antibody.[18]

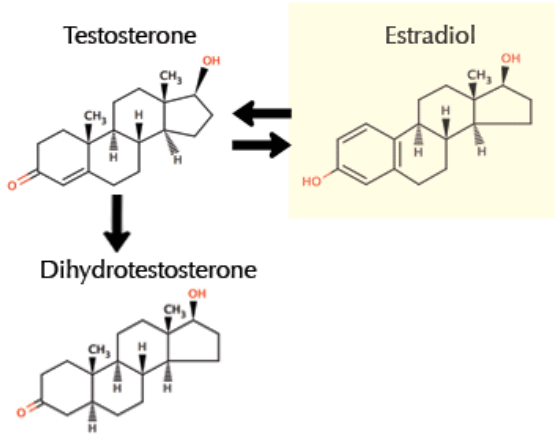
To understand the clinical applications and side effects of anabolic-androgenic steroids, it is important to be aware of the physiology of endogenous androgens in normal males. Testosterone is an androgen hormone, the class of steroids that are responsible for primary and secondary male sex characteristics. Testosterone effects include androgenic (masculinizing) actions and anabolic (tissue building) properties.

The androgenic properties of testosterone are twofold. First, it has an organizational effect involving the development of male characteristics during the late fetal stage and early postnatal life. During development in the male, the earliest function of testosterone is to influence sexual development. The sex characteristics are seen already in the male fetus, where the embryonic testis secretes testosterone, which is important for the development of the fetus. Testosterone virilizes the male urogenital tract in the male fetus. Secondly, during puberty testosterone has an activational effect that includes activation of the male reproductive system and secondary sexual characteristics, such as hair distribution, musculoskeletal configuration, genital size, psychic changes, and sperm production. Androgens stimulate further development of sex organs, such as the prostate and penis. At the onset of puberty, normal levels of testosterone are required for spermatogenesis and sperm maturation.

After the onset of puberty in males, testosterone is responsible for the development of secondary sex characteristics, including spermatogenesis, and functions in many other tissues, including muscle, bone, and immune system. The androgen promoted hair growth and the deepening of the voice are examples of typical secondary sex characteristics. It stimulates enlargement of the larynx and thickening of the vocal cords, which contribute to lowering the pitch of the voice. Testosterone also mediates maturation of facial and body hair and growth of the genitalia. In addition, testosterone promotes libido and sexual potency.

The anabolic effect of testosterone helps the body retain dietary protein (nitrogen retaining), thereby aiding growth of muscles, bones, and skin. These anabolic (myotropic) effects are manifested in an increased protein synthesis and decreased protein catabolism, a larger muscle mass and an increased skeletal maturation and mineralization. In addition, testosterone induces a loss of subcutaneous fat. The anabolic properties of the androgens were reported already in 1935 and studies in the 1950s showed that testosterone administration increased muscle mass in the rat.[19]

Testosterone conversion to estradiol (E2) and dihydrotestosterone (DHT)



The major route of metabolism of testosterone is to inactive products excreted in the urine and bile. The metabolism of testosterone is tissue-specific and implies a unique biological role for many of the products in their tissue of origin. Testosterone metabolizes to two important

biologically active products, nonaromatizable dihydrotesterone (DHT) via the enzyme 5α-reductase and 17β-estradiol (E2) via the enzyme aromatase.

The bioconversion of testosterone to DHT by 5α-reductase occurs primarily in the liver, kidney, skin, and prostate. The testes secrete approximately 20% of the circulating 5α-dihydrotestosterone (DHT) in men. Although the former steroid is the predominant androgen present in the peripheral circulation at a 10-12 fold greater concentration, the local tissue concentration of DHT may be greater, as is its biological potency. Because of high level of expression of 5α-reductase in prostate, DHT in prostate is 5-10 times the peripheral blood concentration.[20] The enzyme aromatase is expressed in Leydig cells, adrenal cortex, adipose, skin-stromal cells, aortic smooth muscle cells, kidney, skeletal muscle cells, and the brain.

Testosterone has both direct and indirect actions. Testosterone exerts its actions directly through the activation of androgen receptors, indirectly through its reduction to 5a-dihydrotestosterone, which also acts on androgen receptors, or indirectly through its aromatization to estradiol and the activation of estrogen receptors. The current model for androgen action involves a multi step mechanism. Upon entry of testosterone into the androgen target cell, binding occurs to the androgen receptor. The androgen receptor, a complex protein made of many parts, is located on the cell surface membrane or cytosol that interacts with the androgen. Upon steroid hormone binding, which may occur either in the cytoplasm or in the nucleus, the androgen receptor binds to specific DNA elements. The binding in the nucleus to specific DNA-sequences results in specific activation of transcription at discrete sites on the chromatin. Ultimately, mRNA synthesis and consequently protein synthesis, which finally results in an androgen response.

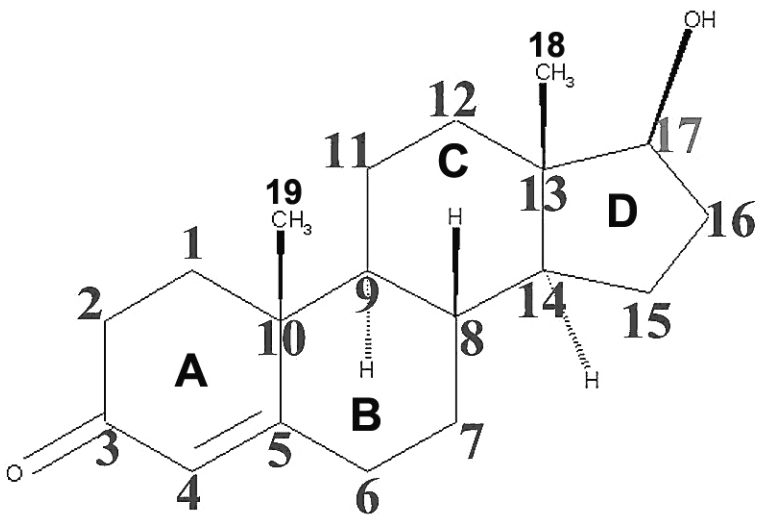
As far as is currently known, there is only one type of nuclear androgen receptor. The androgen receptors on the cells in the body, including the muscle, bone, prostate, and testicles start to diminish and disappear in the presence of decreasing testosterone levels. In a castrated individual, the androgen receptor sites completely disappear. Studies have demonstrated the upregulation of the human androgen receptor by androgens in bone and muscle cells.[21]

The effect of increasing androgen levels increasing AR levels has found usefulness in clinical medicine. Androgen insensitivity syndrome (AIS), caused by mutations within the androgen receptor gene, represents a variety of phenotypes from females with 46,XY karyotype, complete androgen insensitivity syndromes (CAIS), to lesser conditions termed partial androgen insensitivity syndromes (PAIS). Successful treatment with supplemental, supraphysiological, androgen therapy has been described in partial androgen insensitivity (PAIS), androgen-receptor mutation, producing normal virilization.[22]

Steroids are a class of hormones synthesized from cholesterol that share a similar chemical structure.[23] They are any of numerous naturally occurring or synthetic compounds having as basis 17 carbon atoms arranged in four rings. All steroids have the same general tetracyclic ring structure, consisting of three 6-membered rings and one 5-membered ring fused together. The chemical structure of testosterone consists of an androstane four-ring skeleton where the rings are denoted A, B, C and D. This C19 steroid carries two axial methyl groups, C-

18 and C-19. All AAS derivates, like the endogenous androgens, are four-ringed structures with 19 carbon atoms.

Testosterone Structure



The isolation of testosterone and confirmation of its role in normal human development led clinicians to explore the benefits of its use for the treatment of various human disorders. Testosterone itself exhibits a very low bioavailability after oral administration. Early attempts to utilize clinically orally administered testosterone were unsuccessful because it rapidly degraded during its first pass through the liver, resulting in subtherapeutic amounts of the molecule reaching target tissues.

To overcome this problem, the testosterone molecule was modified to produce synthetic androgens that had slower hepatic metabolism and longer systemic exposure. Modification of testosterone was also aimed to enhance testosterone's anabolic effects while reducing its androgenic properties. During the late 1940s and early 1950s, an attempt was made to synthesize a steroid compound that would be anabolic without exhibiting the unwanted androgenic side effects. In 1955, AASs with less, but still some, androgenic properties were developed. Today, no purely anabolic steroids are available. All steroids developed to date have some propensity to show androgenic effects.[24]

The result of these efforts was the development of testosterone analogues. Anabolic androgenic steroids (AAS) have both anabolic and androgenic properties and are synthetic derivates of the endogenous primarily male steroid hormone, testosterone and exert their effects via activation of the same androgen receptor. This includes testosterone, testosterone cypionate, testosterone enanthate, testosterone undecanoate, nandrolone decanoate, oxandrolone, and oxymetholone.

The clinically significant classes of testosterone analogues are the (1) 17 beta-esters (e.g., testosterone propionate), (2) 17 alpha-alkylated anabolic-androgenic steroids (e.g., oxandrolone or oxymetholone), and (3) 19-nortestosterone anabolic-androgen steroids (e.g., nandrolone decanoate). The principal anabolic-androgenic steroids in use in the United States are testosterone cypionate, testosterone enanthate, nandrolone decanoate, oxandrolone, and oxymetholone.

The first class of AAS, called testosterone esters, includes testosterone enanthate, testosterone cypionate, and testosterone undecanoate. Testosterone enanthate and testosterone cypionate are injectable esterifications of testosterone. The esterification delays degradation and prolongs the action by slowing its release into circulation. These esters hydrolyze into free testosterone and can further be reduced to dihydrotestosterone or aromatized to estradiol. Injectable steroids are slowly absorbed into the blood stream without a first pass through the liver. Consequently, the liver experiences a much lower concentration than with oral anabolics. For this reason, most injectable steroids have little effect upon liver function. Most of the common injectable androgens are oil-based preparations containing a mixture of sesame seed oil and alcohol. Administration doses of 100-250 mg at weekly to biweekly intervals appear to maintain adequate serum testosterone levels. The half-life of testosterone cypionate and testosterone cypionate is approximately 7-14 days. The half-life of a given medication is how long it takes the body to get rid of half of the dose.

Oral testosterone undecanoate (Andriol) is a suspension of the ester in oil-filled capsules. The hydrophobic, long aliphatic chain ester in an oil vehicle favors preferential absorption into chylomicrons (fat droplets) entering the gastrointestinal lymphatics and largely bypassing hepatic first-pass metabolism during portal absorption but is only absorbed when ingested with food. Administration is with high doses (160-240 mg) and at frequent daily intervals (3-4 times per day).

The second class is 19-nortestosterone derivates and includes nandrolone decanoate.[25] This class is composed of injectable androgen esters that lack a methyl (CH3) group at the C19 position which lengthens the half-time past that contributed by the esterification alone. The anabolic androgenic steroid nandrolone consists of a C18 skeleton, where the C19 methyl group present in testosterone is missing. Therefore, nandrolone and 19-nortestosterone refer to the same substance. Nandrolone shows higher myotropic (muscle) potency and exhibits a higher affinity for androgen receptors than testosterone.

Nandrolone decanoate is a conjunction of nandrolone and decanoic acid. After injection, nandrolone decanoate is hydrolyzed by an esterase to nandrolone. Pharmacokinetic studies on the intramuscular injection of nandrolone decanoate, 50-200 mg, found a mean half-life of 6-12 days for the release of the ester from the muscular injection depot into the general circulation.[26] The duration of the effect is approximately three weeks.[27] Injection of a *single* 100 mg nandrolone decanoate resulted in suppression of serum testosterone to 1.7-2.4 nM/L (<100 ng/dL) within 7.2-9.2 days for a duration of 11.0-17.5 days.[28] The recommended therapeutic dose of nandrolone decanoate is 2.8 mg/kg/week (intramuscular).[29]

The third class is C 17α-alkyl derivates. Because testosterone is quickly degraded when

administered orally due to the first-pass metabolism in the liver, synthetic steroids have been made more effective by modifying the testosterone molecule. Alkylation diminishes the first passage metabolism in the liver, markedly reducing their capacity to serve as substrates for the metabolizing enzymes in the liver, making these compounds orally active, and with a short half-life, generally less than 12 hours. Due to their short half-life, C17 alkylated steroids administration is on a daily basis if not more often. The modification of these C17 alkylated steroids to survive liver degradation makes them unusually harsh upon the liver.[30] None of the 17α-alkylated steroids is converted to 5α-dihydrotestosterone or 17β-estradiol, although other active metabolites may be formed. C17 alkylated steroids include oxymetholone and oxandrolone.

The androgen receptor is able to discriminate between different agonists and discriminate between different antagonists. There is a lot of literature that androgens have specific effects in the body that is different, one compound from another. AAS other than testosterone, adversely affect the libido (sex drive), energy, sense of well-being, and motivation. A study observed marked irritability and depression within weeks after discontinuation of prescription testosterone despite the continued prescribing of oxandrolone.[31]

The data quantifying the varying degrees of anabolic and androgenic nature between different steroids is also a key to the distinct effects of these compounds at the androgen receptor. The post-binding effects of different steroids demonstrate alternate actions after metabolism. If all anabolic androgenic steroids exhibited similar actions after binding with the androgen receptor, varying anabolic/androgenic activities of the different compounds would not occur. The fact that a compound like oxandrolone has a lower androgenic factor demonstrates an alternate action at the receptor.

The development of AAS compounds originally were for treatment of hypogonadal dysfunction and commencement of delayed puberty in men and for growth promotion.[32] AAS have, however, not always been used for pure medical purposes. Due to their anabolic effects, AAS became vastly popular among athletes, bodybuilders, and power lifters. Controversy raged for decades over the effectiveness of AAS in promoting muscle mass and muscle strength. Despite the admitted illicit use of AAS by athletes, the record breaking in Olympic events, the obvious appearance in musculature enhancement, and more the medical and research community disputed and denied the AAS effects.[33] After a period of scientific controversy, it is now clear that androgenic-anabolic hormones are effective in enhancing performance in sports.[34] Moreover, scientific and official court documents, including secret doctoral theses and scientific reports, demonstrate the positive effects of these and other hormonal drugs on muscle strength and performance in elite sports were common knowledge and had been in practice since the early 1960s.[35]

Serum testosterone level has a positive correlation with protein synthesis that results in lean muscle tissue development (muscle mass and muscular strength),36 sexual desire (libido),37 erythropoiesis,38 bone density,39 and mental cognition and verbal fluency.40 A common finding of studies of hypogonadal young men, as well as older men with age-related declines in testosterone, is reduced lean body mass. The observation that testosterone supplementation in

both young and older men increases muscle mass suggests that testosterone may play an important role in the preservation of muscle mass.

Undoubtedly, the most widely read and influential medical publication in the world is the New England Journal of Medicine (NEJM). In 1996, the NEJM published a study, which firmly established AAS administration increases muscle mass.[41] To overcome some of the pitfalls of previous investigations, Bhasin et al. designed to control for the independent effects of testosterone, training, and diet while the dose of testosterone approached that commonly used in illicit AAS use.

Randomization was to one of four groups: (1) placebo with no exercise, (2) testosterone with no exercise, (3) placebo plus exercise, and (4) testosterone plus exercise. The men received 600 mg testosterone enanthate or placebo weekly for 10 weeks. Testosterone treatment was associated with greater gains in muscle size and strength compared to placebo injections. The effects of testosterone and exercise were additive, resulting in greater increase in fat-free mass, and muscle size compared to either placebo or exercise alone, and greater gains in muscle strength than either nonexercising group. These results demonstrate that testosterone treatment has the ability to increase fat-free mass, muscle size, and strength in healthy men. This important study showed unequivocally for the first time that supraphysiological doses of androgens do have an anabolic effect on muscle mass and strength in eugonadal men.

The baseline characteristics of the groups when the study began were essentially equivalent. The reason for a placebo group is to act as the control in the investigation. A significant change in the treatment or intervention group in comparison to the control at the conclusion, or during, the study requires explanation and addressing. On the biochemical part of the study, the results were serum total testosterone levels significantly increased. More importantly, there was a significant suppression of serum luteinizing hormone (LH) levels in the testosterone treatment groups but not the placebo treatment groups. In this case, the prognosis of the testosterone treatment groups has changed due to the intervention. This is an adverse event and indicates HPTA suppression. The testosterone treatment group has AAS induced hypogonadism.

The investigation by Bhasin is not a clinical study for AAS treatment in certain disorders but rather it is a study to separate out the effects of progressive resistance exercise and AAS on muscle mass and strength. There is agreement that testosterone replacement increases fat-free mass and maximal voluntary strength in healthy, hypogonadal men.[42] Testosterone increases fractional muscle protein synthesis.[43] In well-controlled studies of eugonadal, young and older men testosterone shows strong linear relationships of dose with muscular size and strength throughout and beyond the physiological range.[44] In a testosterone dose–response study, increasing doses of testosterone enanthate were associated with dose-dependent changes in serum total and free testosterone concentrations, fat-free mass (FFM), and muscle size. Of the models tested, a linear model best described the relationship between testosterone dose and steady state concentrations. Thus, the research aim above is to determine whether testosterone administration does cause an increase in muscle mass and strength.

The list of AAS adverse effects is legendary, though most lack empirical support. Anabolic-androgenic steroids have effects in several organ systems. The frequency of occurrence and severity of side effects are quite variable and depend on numerous factors such as the type of drug, dosage, duration of use, and the individual sensitivity of the response. The potential adverse effects of anabolic-androgenic steroids include cardiovascular, hepatic, endocrine, and psychological.[45]

Moderately supraphysiological doses of testosterone, such as those used in male contraception trials, have caused acne, gynecomastia, increased or decreased sexual interest, mild behavioral changes, reduction in the circulating concentrations of high-density lipoprotein cholesterol, prostatic enlargement, testicular atrophy, infertility, and azoospermia.[46]

It affects circulating lipids by stimulating hepatic endothelial triglyceride lipase, the enzyme responsible for transporting high-density lipoprotein (HDL)-cholesterol into hepatocytes. This effect lowers circulating levels of HDL-cholesterol and may contribute to higher levels of serum triglycerides and low-density lipoprotein (LDL) cholesterol in men.[47] The question of whether exogenous androgens, at physiological or slightly supraphysiological doses increase or reduce the risk of cardiovascular disease remains controversial. Although changes in lipoprotein levels that are considered atherogenic have been observed, changes in lipoprotein levels that may be beneficial, such as a decrease in lipoprotein(a) have also been observed.[48] The consistent finding that low testosterone concentrations in men are associated with common risk factors of coronary artery disease such as a pro-atherogenic lipid profile, systolic and diastolic hypertension, hyperinsulinemia, android obesity, and high fibrinogen levels may indirectly suggest that exogenous testosterone would reduce the risk of cardiovascular disease in some men.[49]

The serious adverse hepatic effects associated with prolonged use of some androgens, such as cholestasis, peliosis hepatis (blood-filled hepatic cysts), hepatocellular hyperplasia, hepatic adenomas, and hepatocellular carcinoma seem to be mostly restricted to users of 17a-alkylated derivatives of testosterone.[50] Treatment with 17-alkylated androgens has consistently been associated with disturbances in liver function, ranging from a mild increase in liver enzymes to jaundice. There are case study descriptions of hepatic and splenic peliosis as well as hepatocellular adenoma and carcinoma following therapy with alkylated compounds.

The importance and value of observational material from illicit AAS users has proven correct repeatedly. Athletes and bodybuilders relate a significant heterogeneity in response to AAS anabolic actions. Individuals cite identical illicit AAS use and progressive resistance training but with marked differences in improvement in muscle mass and strength. These anecdotal reports are similar to published reports studying AAS administration for their properties to increase muscle mass ands strength. Despite the high degree of overall correlation between testosterone dose and changes in FFM and muscle size, there is considerable heterogeneity in individual responses to a given testosterone dose.[51] Bhasin's study is an important watershed moment because it was the first well-designed placebo-controlled clinical trial that pharmacological testosterone doses increase muscular size and strength even in eugonadal, normal, men. The basis for Bhasin’s study is the observation on muscle mass and strength with illicit AAS use. Equally important is the observation and reporting from any illicit

AAS user for a period of marked muscle loss and other signs and symptoms after stopping the use of AAS.

Numerous studies have discussed the use of AAS in the treatment of sarcopenia,[52] COPD,[53] HIV+ males,[54] chronic glucocorticoid administration,[55] osteoporosis,[56] and hemodialysis.[57] These studies are in eugonadal (including low normal) or abnormal low testosterone levels. The results uniformly demonstrate an increase of muscle mass, muscle strength, and decreased adiposity, though the magnitude of improvements varied considerably among the studies.

The critical difference between investigations that elucidate a physiological process and investigations that translates to clinical application is that the former do not take into consideration the overall health of the individual, in this case homeostasis, while the latter has as its only concern the health and welfare of the individual. The difference is critical when translating research findings to clinical applications. The Bhasin et al. study is not a template for the clinical application of AAS treatment. Far from it, the findings of the study is that testosterone, and by implication AAS, is a modulator of body composition. Any clinical application must take into consideration all of the physiological processes of the body and not one in complete isolation and definitely not ignoring or dismissing adverse events from a drug administration. The most debilitating and common adverse effect is not during AAS administration but that which occurs after AAS cessation. However, since AAS adverse effects during their administration necessitate and require their discontinuation this adverse effect is unavoidable.

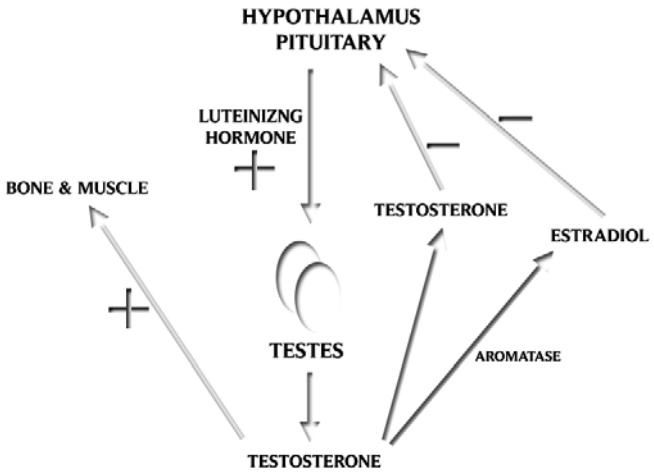
The take home message from this is that AAS administration is for a limited duration, typically for a few months, not long term. In clinical studies, discontinuation of treatment is usually due to cholesterol or liver function changes. Regardless of the reason for early discontinuation in clinical studies, AAS cessation occurs with the occurrence of the most debilitating side effect, anabolic steroid induced hypogonadism (ASIH).

- 2 -

HYPOTHALAMIC PITUITARY TESTICULAR AXIS (HPTA)

The HPTA is a dynamic feedback loop.[58] Homeostasis is the process by which an organism maintains constant internal conditions in the face of a varying external environment. The hypothalamic pituitary testicular axis (HPTA) is the homeostatic system responsible for maintaining, supporting, and ensuring reproduction, bone density, muscle mass, and other important and vital physiological and psychological processes.

Structural components of the HPTA are the hypothalamo-pituitary, testicles, and androgen receptor (AR) located on certain end organs (prostate, bone, and muscle). The medical and scientific literature demonstrates interdependent communication must be at a certain functional level between the hypothalamo-pituitary, testes, and androgen receptor (AR) to maintain HPTA homeostasis. The major hormones of the hypothalamic pituitary testicular axis are gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin, testosterone, dihydrotestosterone (DHT), and estradiol.



In males, luteinizing hormone (LH) secretion by the pituitary positively stimulates testicular testosterone (T) production. The pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus stimulates LH secretion. Regulation of the secretion of GnRH

and LH is by the negative feedback of testosterone and estradiol at the level of the hypothalamo-pituitary. Estradiol has a much larger, inhibitory effect than testosterone, being 200-fold more effective in suppressing LH secretion. 5α-reduction, DHT, does not appear to play a significant role in the negative feedback effect. Absent LH, there is no testicular testosterone production.

Science is the observation, identification, description, experimental investigation, and theoretical explanation of the natural world. The scientific method as it applies to medical research is first to an understanding of normal physiology, to investigate and explain changes from normal, and to apply treatments or therapies for these abnormal changes. The latter done in the goal to decrease morbidity and mortality. The correct application of the scientific method requires attention to underlying scientific theory and law. The bases of modern biology are on several great ideas, or theories of which there are the Cell Theory and Homeostasis. Failure to account for these will negate any study conclusion or finding unless expressly qualified.

Cell Theory, also known as cell doctrine, states that all eukaryotic organisms are composed of cells, and that cells are the smallest independent units of life. This Cell Theory has been influential in shaping the biological sciences ever since, in 1838/1839, the botanist Matthias Schleiden and the zoologist Theodore Schwann stated the principle that cells represent the elements from which all plant and animal tissues are constructed. Some 20 years later, in a famous aphorism, Omnis cellula e cellula, Rudolf Virchow annunciated that all cells arise only from pre-existing cells. The Modern Cell Theory consists of three statements based on a large body of scientific research: (1) the cell is the fundamental unit of structure and function in living things, (2) all living things are composed of cells, and (3) cells come from preexisting cells.

Firmly embedded in all biological disciplines is the cell doctrine, which acts as a general paradigm of organism and tissue construction and function. Further, cell theory states the characteristics of life are living things acquire and use energy and produce wastes; living things reproduce, grow, and develop; living things evolve; living things respond to stimuli; living things maintain a state of homeostasis; and all living things are made up of atoms and molecules. The one characteristic that is of a central concern is homeostasis. Homeostasis is a characteristic of life, a basic underlying component of cell theory.

Homeostasis is the existence and maintenance of a relatively constant environment within the body; self-regulation, the ability or tendency of an organism or a cell to maintain internal equilibrium by adjusting its physiological processes and their variables, such as body temperature blood pressure, or the hormonal milieu (i.e., reproductive, thyroid, and metabolic) which are important for the survival or health of living organisms. Homeostasis is the process by which an organism maintains constant internal conditions in the face of a varying external environment.

Although the human body as a whole is adapted to cope with a variable external environment, most of the individual cells of the body are much less tolerant of change. Only a small minority of cells in a multicellular organism are actually in direct contact with the external environment. The vast majority of the cells are sheltered from the outside world by the buffer zone of the extracellular fluid, the body fluid that surrounds the cells.

This internal environment serves as the interface between the external environment and the cells. When conditions outside the body change, changes occur in the composition of the extracellular fluid, which in turn affects the cells. A variety of mechanisms has evolved that maintain the composition of the ECF within a narrow range of values. Following any change in the internal environment is a response that attempts to restore the normal condition. The coordinated response of the body in order to maintain internal stability is the process known as homeostasis. Homeostasis and the regulation of the internal environment are central precepts of physiology and create an underlying theme. Failure to maintain homeostasis disrupts normal function.

Homeostasis is most associated with health and disease. Homeostasis in an organism is constantly threatened. Failure to respond effectively can result in disease or death. Disease is a disturbance of homeostasis or steady state within an organism. Disease is an impairment of the normal state of the living animal or plant body or one of its parts that interrupts or modifies the performance of the vital functions and is a response to environmental factors (as malnutrition, industrial hazards, or climate), to specific infective agents (as worms, bacteria, or viruses), to inherent defects of the organism (as genetic anomalies), or to combinations of these factors.

Humans have developed certain mechanisms to ensure homeostasis. Dynamic equilibrium or homeostasis results from the ability of organisms to detect and respond to stimuli. Performance of this is by means of multiple dynamic feedback mechanisms. Those that are most well known are the existence of positive and negative feedback loops. A feedback mechanism is a process where the level of one substance or activity of an organ or structure influences another substance or structure in some manner.

All humans need "coordinating systems to regulate and integrate the function of differentiating cells." Two mechanisms perform this function in higher animals: the nervous system and the endocrine system. Neuroendocrinology is the study of the interaction between the nervous system and the endocrine glands and their secretions. The hypothalamus and pituitary serves as the body's primary interface between the nervous system and the endocrine system. The hypothalamus is the part of the brain that regulates several aspects of endocrine function. The pituitary gland is as small as a pea, located at the base of the brain. The hypothalamus controls the pituitary gland by secreting locally acting hormones that act on the pituitary gland, which secretes a wide range of hormones.

Hormones are molecules that act as signals from one type of cells to another. Endocrinology is concerned with the study of the biosynthesis, storage, chemistry, and physiological function of hormones and with the cells of the endocrine glands and tissues that secrete them. The endocrine system acts through the release (generally into the blood) of chemical agents and is vital to the proper development and function of organisms. The endocrine system consists of several glands, in different parts of the body that secrete hormones directly into the blood rather than into a duct system. Hormones have many different functions and modes of action; one hormone may have several effects on different target organs, and, conversely, one target organ may be affected by more than one hormone.

The testis has both endocrine and gametogenic functions. The Sertoli cells and Leydig cells are the primary components of the testes. Smith first described the involvement of the pituitary gland in the control of spermatogenesis in 1927.[59] Using the classic endocrine technique of gland removal followed by replacement of the postulated active substances, he demonstrated the importance of pituitary factors in the stimulation of testicular growth and spermatogenesis in the rat by observing the effect of hypophysectomy, pituitary resection, and subsequent administration of pituitary extracts.

Hormones secreted from the hypothalamus and transported in the hypophyseal portal blood regulate the endocrine activity of the pituitary. The proximate regulator of testosterone synthesis and secretion is the pulsatile release of gonadotropin releasing hormone (GnRH), produced in neurons located diffusely throughout the hypothalamus. Two pituitary hormones are involved, with separate effects on the Leydig cells (androgen production) and on Sertoli cells (spermatogenesis).[60] Current understanding is for the dual control of the endocrine and spermatogenic functions of the testes by LH and FSH. Gonadotropin secretion, LH and FSH, is under the overall stimulatory control of GnRH.

The control of testicular function begins with the pulsatile release of gonadotropin releasing hormone, GnRH, from the hypothalamus. Transportation of GnRH is by the hypothalamic-pituitary portal system to the pituitary where it affects the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Following release from the pituitary gland, transportation of LH and FSH are via the systemic circulation to the testes.

The pattern of both LH and FSH secretion in the peripheral circulation is pulsatile.[61] The pulsatile nature of GnRH secretion is crucial for the maintenance of gonadotroph responsiveness, preventing receptor down-regulation and subsequent fall in LH and FSH secretion.[62] LH feeds forward on testicular Leydig cells to stimulate the time-delayed output of sex-steroid hormones.[63] Leydig cells release a class of hormones called androgens. They secrete testosterone, androstenedione, and dehydroepiandrosterone (DHEA). In young adult males, secretion of testosterone is in an episodic fashion in response to an LH stimulus.[64] The result is an overall diurnal rhythm in serum testosterone, which is maximal in the early morning hours and minimal in the evening.[65] There is no clear diurnal rhythm for LH in most adult men.[66] FSH, after release into the systemic circulation, binds specifically to the Sertoli cells in the testes and stimulates the production of a number of proteins, including inhibin that along with testosterone from the Leydig cell induces and maintains spermatogenesis. Sertoli cells are responsible for establishing and maintaining the process of spermatogenesis, ending in the release of spermatozoa.

The medical literature has demonstrated interdependent communication must be at a certain functional level between the hypothalamo-pituitary, testes, and androgen receptor to maintain HPTA homeostasis. Medical and scientific literature demonstrates the AR is critical in the homeostasis of the HPTA. The AR is located throughout the body, particularly bone and muscle, and is a complex protein made of many parts located on the cell surface membrane that interacts with the androgen. Studies have demonstrated the up-regulation of the AR by androgens in bone and muscle cells.[67]

Neurological inputs and feedback control by both the pituitary hormones themselves and circulating products of the endocrine systems influence hypothalamic secretion of GnRH. The frequency of GnRH pulses seen by the pituitary along with negative feedback signals is the determinant of the relative amounts of LH or FSH released from the pituitary. Both the pituitary hormones themselves and circulating products of the endocrine systems controlled by those hormones can regulate hypothalamic secretion, usually through feedback inhibition. In the male, both testosterone and estradiol exert dual negative feedback actions, at the hypothalamus to decrease GnRH pulse frequency and amplitude and at the pituitary to decrease responsiveness to GnRH.[68] Furthermore; estradiol is 200-fold more effective than testosterone in suppressing GnRH-driven gonadotropin secretion.[69]

Pituitary secretion of LH and FSH is controlled by hypothalamic secretion of GnRH, the secretory products of the testes (testosterone and inhibin), and metabolism of testosterone (estradiol). Inhibin from Sertoli cells of the testicles has a negative feedback on FSH secretion. This relationship between inhibin and FSH is observed across the physiological range in normal men. This strongly suggests that inhibin is an important component of the afferent arm of the feedback loop from the testis, selectively regulating FSH secretion. Although testosterone is the major steroid secreted by the testis, it has been long recognized that estradiol is involved in the regulation of gonadotropin secretion.[70] The plasma estradiol mainly arises from aromatization of testosterone.

Estradiol is an important feedback regulator of LH and, thereby, testosterone secretion in men. In fact, much of feedback inhibition of LH secretion by testosterone can be accounted for by its bioconversion to estradiol. Studies of sex steroid regulation of gonadotropin secretion in the human male have focused primarily on the respective site(s) of negative feedback of testosterone and estradiol. Studies provide evidence of differential regulation of gonadotropin secretion by testosterone in the human male. Testosterone exerts both direct and indirect feedback on LH secretion, whereas its effects on FSH appear to be mediated largely by aromatization to estradiol.[71]

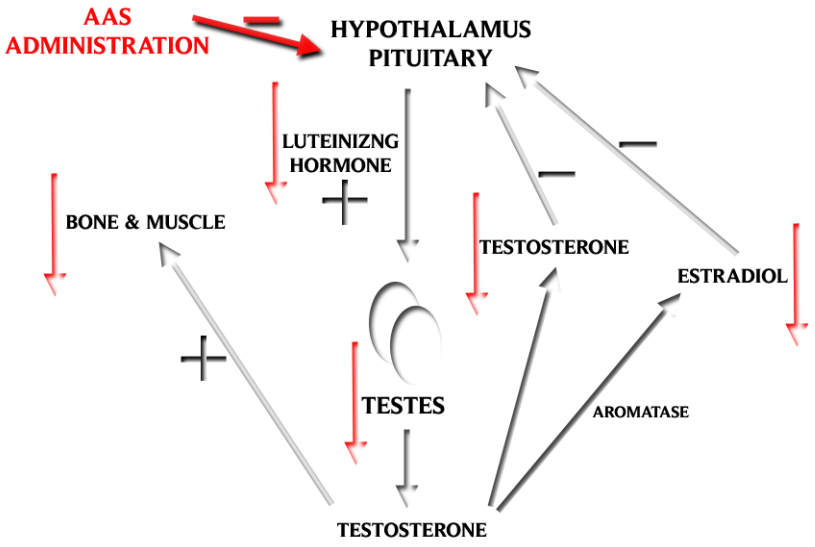
In summary, the level of androgens, testosterone, within the body is under the control of a dynamic feedback loop. The hypothalamus-pituitary secretes hormones, LH & FSH, which positively stimulate the testicles and production of spermatozoa and testosterone. Regulation of the secretion of LH is by the negative feedback of testosterone and estradiol at the level of the hypothalamus and pituitary.[72] Testosterone can inhibit the secretion of both LH and FSH, while inhibin inhibits primarily the secretion of FSH. These findings provide the basis for the current understanding of the dual control of the endocrine and spermatogenic functions of the testes by LH (via production of testosterone) and FSH (via production of inhibin).

- 3 -

HYPOGONADISM
ANDROGEN INDUCED HYPOGONADISM (AIH)

Hypogonadism is a disturbance of HPTA homeostasis. Hypogonadism is inadequate gonadal function, as manifested by deficiencies in spermatogenesis and/or the secretion of testosterone. AAS, including testosterone, licit and illicit, administration induce a state of hypogonadism that continues after their cessation. This state is present during their administration but typically becomes symptomatic or manifest after AAS cessation. To date, all compounds classified as androgens or anabolic steroids prescribed clinically cause a negative feedback inhibition of the hypothalamic pituitary testicular axis, suppress endogenous gonadotropin secretion, and as a consequence serum testosterone.

Androgen, anabolic steroid, induced hypogonadism (AIH) is the functional incompetence of the testes with subnormal or impaired production of testosterone or spermatozoa due to administration of androgens or anabolic steroids. AIH results from an abnormality in the normal functioning of the hypothalamic-pituitary-testicular axis (HPTA), from a negative feedback inhibition of one of the hormone secreting glands, causing a cascading unbalance in the rest of the axis.



Androgen, anabolic steroid, induced hypogonadism (AIH) occurs in one-hundred percent of individuals upon AAS cessation. There is not a single study within the peer-reviewed literature demonstrating an immediate return of HPTA homeostasis upon AAS cessation. AAS, licit and illicit, induce a state of hypogonadism that continues after their cessation. The only variable is the duration and severity of AIH. AIH, as a form of hypogonadism, is a real disease with potentially serious consequences.

Declining, or suppressed, circulating testosterone levels because of either pathophysiological or induced hypogonadal conditions can have many negative consequences in males. There is a direct association between hypogonadism (decreased levels of testosterone) and a number of signs and symptoms, most notably body composition changes (decrease in muscle mass and increase in fat mass), decreased muscle strength, bone loss, increased cardiovascular risk, sexual dysfunction (decreased libido, decreased spontaneous erections, decreased ejaculate, erection dysfunction, decreased sexual fantasies, and anorgasmia), decreased cognitive abilities (memory and concentration), sleep disturbances,[73] adverse psychological effects (depression, low self esteem, guilt, increased stress, and anhedonia), sleep disturbances, and constitutional symptoms (general fatigue, agitation/motor dyskinesia, and decreased appetite[74]). Reports of symptoms following use of illicit androgens also include suicidal ideation and suicide.

Disease is an impairment of the normal state or one of its parts that interrupts or modifies the performance of the vital functions. Disease is a disturbance of homeostasis or steady state within an organism. The disease spectrum is the range of the disease states represented by the diseased individuals (acute vs. chronic or convalescent cases, mild vs. severe cases, clinical vs. subclinical). According to one popular medical dictionary, "disease" means "any deviation from or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown."[75] An asymptomatic condition does not exclude disease since the presence of signs (laboratory, radiological, etc.) will connote disease. These include diseases such as hypertension, hypercholesterolemia, hypogonadism, and infertility.

Every disease has a range of manifestations and a natural history that varies from individual to individual. Pathophysiology is a term that refers to the disorder or breakdown of the human body's function. Three aspects of a disease process form a framework for understanding pathophysiology. They are the cause or etiology of the disease, the pathogenesis of the mechanism of its development, and clinical manifestations representing the structural and biochemical alterations in the body and the functional consequences of these changes.[76]

The most obvious medical indication for androgen administration is male hypogonadism. Men with hypogonadism are unable to synthesize adequate quantities of androgens and need long-term androgen replacement to maintain sexual behavior, androgen-dependent physiological processes, secondary sexual characteristics, and mental health. Under these conditions, androgen administration is a life long commitment. However, under many other different circumstances androgen administration is for a self-limited duration.

AIH OBSERVED WITH ILLICIT AAS USE OCCURS WITH CLINICALLY PRESCRIBED AAS

There is not a single study within the peer-reviewed literature demonstrating an immediate return of HPTA homeostasis upon AAS cessation. Publication of dose-response relationship studies between AAS administration, AAS cessation, and HPTA normalization, serum testosterone and luteinizing hormone, have yet to occur. The adverse effects of androgenic-anabolic steroids on the hypothalamic-pituitary testicular axis are present in the peer-reviewed literature for over fifty years.

Boje was the first physician to suggest, in 1939, that AAS might enhance athletic performance, but he was also the first to forewarn athletes of potential health effects of steroids.[77] Due to their anabolic effects (e.g. increases in muscle mass, strength, and endurance and faster recovery from injuries), AAS have become vastly popular in the athletic community. In athletes, the use of illicit AAS may result in a functional type of hypogonadotropic hypogonadism. Studies of illicit AAS use have consistently shown the suppression of the HPTA after AAS cessation.

A number of papers document the adverse effects on the HPTA after illicit AAS use. Published literature extensively demonstrates hypogonadism occurring after illicit AAS cessation.[78] In 1981, Clerico et al found a dramatic suppression of serum gonadotropin and testosterone levels in athletes given methandrostenelone. The serum testosterone levels did not return to normal even after the gonadotropin levels returned to normal.[79] In 1985, studies on the influence 26 weeks of self-administration of anabolic steroids and a follow-up period of 16 weeks after drug withdrawal showed a major decrease in serum FSH and LH concentrations that returned to control levels following drug withdrawal. However, serum testosterone concentrations stayed at low levels during this follow-up period, indicating long-lasting impairment of testicular endocrine function.[80] In a reported study of an elite athlete, self-administering AAS (actually 53 mg/day) for one year showed after AAS cessation low LH, FSH, and T levels. The author's conclusion was AAS administration affects the function of the pituitary and leads to long-lasting impairment of testicular endocrine function.[81]

In 2003, a retrospective study examined the effects of illicit AAS on a population in which the mean time off steroids was 43 months with the minimum length of time 1 year and the maximum 10 years.[82] The study found 100% of the individuals to have HPTA dysfunction, 13/15 ex-AAS users were in the lower 20 percent of the normal reference range for testosterone and 2/15 were below the normal range (345-864-ng/dL) with 259-ng/dL and 190-ng/dL, respectively.

The argument that endocrine responses to illicit AAS use are transient and recover without intervention is one that has no basis in published literature. This opinion has an apparent basis in the return of spermatogenesis after AAS cessation. The return of spermatogenesis is not the equivalent of a return of normal serum testosterone levels. Regardless, the return of spermatogenesis does not return immediately after AAS cessation, but returns after an unknown duration. Spermatogenesis does return in many, not all, after cessation of illicit AAS use.

The effects on testes and sperm production are due to AAS induced suppression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. The LH and FSH levels, regulating testosterone production and spermatogenesis, typically return to normal after withdrawal of the AAS, whereas the concentration of endogenous testosterone remains reduced. However, spermatogenesis returns in the presence of hypogonadal testosterone levels. Thus, spermatogenesis does not equate to normal serum testosterone levels. The basis for the belief that HPTA normalization returns in users of illicit AAS after AAS cessation is on spermatogenesis, not serum testosterone.

In 1989, Knuth et al. examined retrospectively semen parameters of 41 bodybuilders with a history of illicit AAS administration and 41 consecutively recruited normal volunteers not using any steroids or other drugs.[83] Although only five of the normal volunteers had sperm counts below the lower normal limit of 20 x 10(6) sperm/mL, 24 of the bodybuilders showed subnormal values. There was a significant reduction in percentages of motile and normally formed sperm in bodybuilders compared with normal volunteers. In those bodybuilders who had stopped consumption of anabolic steroids greater than four (4) months previously, sperm numbers were in the normal range. Gazvani et al. followed a small series of individuals treated for infertility. Conservative management consisted of discontinuation of the offending steroid(s) and an end-point of normal semen density. The time intervals to normal spermatogenesis were from 9-22 months.[84]

The academic and medical communities have erroneously assumed that only the use of large AAS doses and simultaneous multiple AAS use for a prolonged duration results in hypogonadism after AAS cessation. The belief, unsupported and unsubstantiated, is prescription AAS would give no reason for concern. The actual nondisputed fact is to the contrary. Published literature uniformly and definitively finds AAS administration induces a state of hypogonadism after AAS cessation. Documentation in peer-reviewed literature shows AAS prescribing with clinical doses and durations to cause both HPTA suppression and hypogonadism after AAS cessation. It is a maxim that after AAS administration, HPTA suppression follows, with the variables being the duration and severity.

In 1982, there was publication of the HPTA suppressive effects of nandrolone.[85] During a pilot study regarding the possible beneficial effect of the anabolic steroid nandrolone decanoate on bone metabolism in patients with rheumatoid arthritis, study findings include a significant decrease in the serum levels of testosterone. This study demonstrates HPTA recovery was incomplete three months after cessation of nandrolone decanoate administration. Likewise, in 1989, there was reporting of anabolic steroid-associated hypogonadism to have occurred in hemodialysis patients administered nandrolone decanoate.[86] Twenty-three patients receiving anabolic steroids showed significantly lower testosterone values than did patients without anabolic steroid administration. The authors warned that anabolic steroid administration is a possible cause for uremic hypogonadism.

Administering a course of the oral (C17α-alkyl derivates) anabolic steroid stanozolol in a clinical dose for 14-day resulted in a marked reduction in serum testosterone levels accompanied by reductions in LH levels.[87] Administration of the oral anabolic steroid oxandrolone (5 days at

15 mg/day) resulted in a significant reduction of serum total testosterone and free testosterone concentrations compared to baseline.[88]

Countless publications study the use of testosterone as a male contraceptive agent. The simplistic reason for this is that exogenous administration will cause HPTA suppression, a decrease of sex hormones that includes endogenous testosterone production and the gonadotropins, both follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH). The absence of FSH leads to infertility, contraception, or diminished spermatogenesis. This is an induced state of hypogonadism, infertility. The absent or decreased testicular testosterone production is replaced by its external administration. The individual does not experience the adverse effects of hypogonadism secondary to decreased serum testosterone because of exogenous testosterone administration. This does not take away from the fact that the patient is in a state of induced hypogonadism for the express purpose of contraception.

Birth control studies with testosterone administration in physiological as well as subphysiological doses demonstrate HPTA suppression.[89] Studies conducted by World Health Organization have demonstrated complete recovery of the hypothalamic pituitary testicular axis (HPTA) after administration of supraphysiologic doses of testosterone for a year. The study tested the use of testosterone enanthate 200-mg intramuscular/week for 12 months as a male contraceptive. The primary outcome is spermatogenesis, not testosterone production. The "complete recovery" referred to is spermatogenesis and not serum testosterone.

According to the study, recovery information is available for 85% of the men; the sperm concentration of 84% of these men has returned to 20 million/ml and 46% to their own baseline level. The median time to recovery to 20 million/ml was a range of 2.8-9.5 months. Equivalent data for return to subject's own geometric mean baseline sperm concentration are a range of 4.0-13.9 months. Thus, the data from the study affirm that the return of normal spermatogenesis may take over a year. The salient point is that after AAS cessation there is a period of recovery.

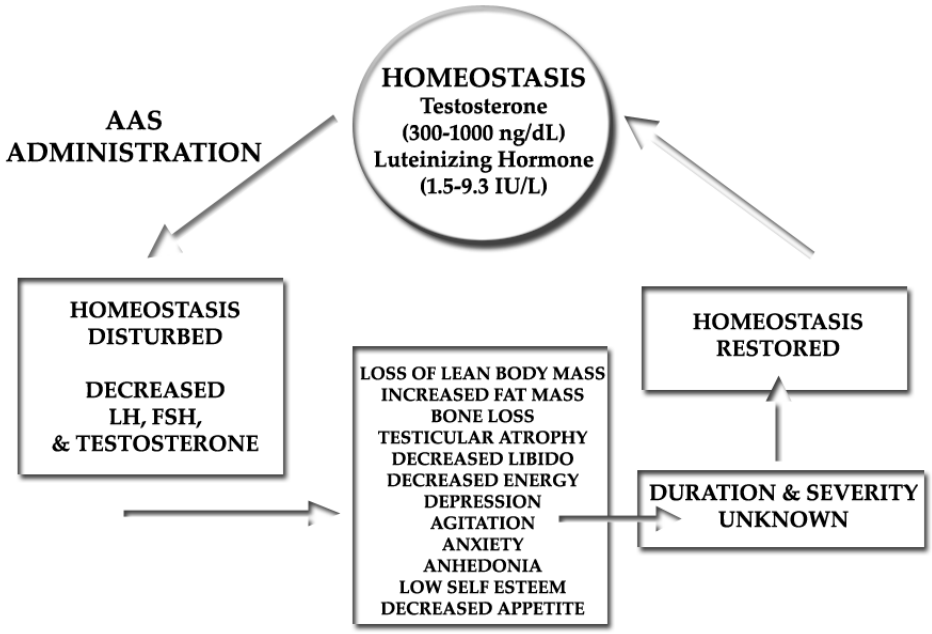
Male contraception studies with 19-nortestosterone, nandrolone, demonstrate the continued suppression of serum testosterone from control levels for greater than 15 weeks after nandrolone cessation.[90] Other data available from the development of nandrolone decanoate for male contraception indicate that reversal of effects can take up to twelve months after discontinuation of the drugs.[91]

Demonstration that the return of spermatogenesis does not equate with the return of normal serum testosterone is clear from a study on assisted reproduction. In 2003, there was a reported case study of a male patient with azoospermia receiving the prescription androgens testosterone enanthate and oxandrolone, undergoing assisted reproduction.[92] Initial treatment was discontinuation of testosterone enanthate but not oxandrolone. Three months after discontinuation of testosterone enanthate alone, the serum T level was 30-ng/dL. In the hope of inducing spermatogenesis both prescription AAS, testosterone enanthate and oxandrolone, were discontinued. Three additional months, six months total, after discontinuation of both androgens the serum testosterone level, 134-ng/dL, was still well below the normal range (270-1100 ng/dL). This is the identical clinical situation described above for the return of spermatogenesis but not the serum testosterone.

Lastly, excerpts from the 2000 PDR for the FDA approved labeling of AAS contain the following. Clinical pharmacology includes, "Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. . . . They suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes." Adverse reactions in men are "Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence . . . ."

Contradictory to the claim for no period of hypogonadism after AAS cessation is that every published paper in print demonstrates a period of hypogonadism for unknown duration and severity after AAS cessation. There is not a single paper or study demonstrating an absence of hypogonadism after AAS cessation. By all available published literature, AAS administration induces a state of hypogonadism after their cessation. Contrary statements go against every published article on HPTA physiology, basic rudimentary endocrinology knowledge, PDR information, and are an effrontery to layperson and professional, alike.

AIH EXHIBITS THE SAME SIGNS AND SYMPTOMS OBSERVED IN CLASSICAL HYPOGONADISM



Another argument offered is that the effects (signs and symptoms) cited in the published literature for hypogonadism are from long-standing disease and not those observed from acute changes after AAS cessation. Stated otherwise, hypogonadal signs and symptoms observed with classical hypogonadism do not occur in the period immediately following AAS cessation. Also, stated previously is that to date there are no AAS dose-response studies for HPTA normalization and associated adverse effects in published literature. There have been countless missed opportunities for the observation, recording, and reporting of HPTA normalization and

associated adverse effects after AAS cessation as evident by the number of AAS clinical studies published. Unfortunately, for those that do research in an unscientific manner the published literature conclusively demonstrates hypogonadism occurs one-hundred percent of the time after AAS cessation and the adverse effects of AIH are the same seen for hypogonadism and may even be much worse. These effects include those that directly affect the primary outcomes of published AAS studies.

There are several models used to determine the effects of hypogonadism. Spontaneous male hypogonadism is a relatively rare disorder and does not produce data readily available or reproducible. Iatrogenic hypogonadism does occur. The model of studying the adverse effects after AAS cessation in AAS clinical studies has largely been lost. Another model utilizes either surgical or biochemical castration to assess the effects of abrupt testosterone withdrawal. Obviously, surgical castration is ethically impermissible. Biochemical castration involves the use of drugs that reversibly produce hypogonadism.

Pharmacologically induced hypogonadism provides an opportunity to examine these questions within a controlled experimental design. Biochemical castration or androgen deprivation therapy (ADT) is a form of therapy in the treatment of prostate cancer that is androgen-sensitive. GnRH is the hypothalamic hormone acting upon the pituitary to produce FSH and LH. Studies found that the use of GnRH analogs is an effective form of androgen deprivation therapy.[93] Treatment with gonadotropin-releasing hormone (GnRH) analogs inhibits pituitary secretion of LH and thus testicular production of testosterone.[94]

In stark contrast and marked contrast to the published literature on AAS clinical studies, researchers using GnRH induced hypogonadism recognize the importance and relevance to determine the time to normalization of serum testosterone after withdrawal of ADT. Cognizant for the effects of hypogonadism, investigators advocate the measurement of serum testosterone in all men until normalization after ADT cessation.

Nejat et al prospectively measured serial serum testosterone at 3-month intervals in men after withdrawal of androgen deprivation therapy. The number of months to return to normal serum testosterone 270 ng/dl or greater, was calculated for each patient. Median time to normalization of testosterone was 7 months (range 1 to 58). The results found ADT has an effect on serum testosterone that extends beyond the cessation of treatment.[95] Oefelein found after a single 3-month GnRH agonist injection the median duration of serum testosterone $\leq$200 ng/dL was 6 months.[96] Median duration of hypogonadal symptoms was 13.6 months and was for a longer duration than the product labeling suggests. Resolution paralleled the gradual return of serum testosterone to baseline values. Padula et al. sought to identify pretreatment predictors that correlated with the time to testosterone normalization after ADT cessation.[97] The findings on a median duration of six months ADT is testosterone levels often remain depressed for extended periods in those with lower baseline testosterone levels.

The same model that has utility in the treatment of prostate cancer is now used widely in the study of the adverse effects of hypogonadism. Studies on the adverse effects of hypogonadism include body composition changes, cardiovascular, bone loss, psychological (depression, libido, arousal, etc.), and others. Testosterone manipulation in eugonadal men has

produced results consistent with the earlier hypogonadal studies. The signs and symptoms observed with hypogonadism in long-term studies are replicated in short-term studies. With this in mind, these results are a foreboding of what has taken place, is taking place, and will continue until recognition of the importance of androgen, anabolic steroid, induced hypogonadism.

Body Composition

The idea that secretions of the testis might regulate body composition is as old as humanity itself. It is currently accepted practice that androgens modulate body composition. Investigations into the effects of testosterone on body composition have their basis on prior evidence of the nitrogen-retaining properties of testosterone.

Hypogonadism is an important modulator of body composition.[98] Hypogonadal men have higher fat mass and lower fat-free mass compared to age-matched eugonadal controls. Hypogonadal adult men have greater deposition of central fat compared to age and body mass index (BMI)-matched eugonadal men. In a study utilizing computed tomography (CT) scans to quantify site-specific adiposity, hypogonadism was associated with more subcutaneous fat deposition, and a trend for more visceral fat compared to eugonadal men. Epidemiological studies have revealed an inverse relationship between serum-free testosterone concentrations and intraabdominal fat, measured by computed tomography (CT) scan. These data indicate that lower testosterone levels correlate with increases in fat mass and suggest that lower testosterone levels have a contributory role in promoting central fat accumulation. There is also correlation of low testosterone levels with decreased strength of knee extension and flexion in older men.

Studies of the effects of testosterone on body composition in eugonadal men have led to important information with regard to changes in adiposity and lean body mass in the setting of testosterone administration. Earlier studies demonstrate the improvements in body composition obtained during testosterone administration, are lost after testosterone cessation.

In 1990, the World Health Organization study tested the use of testosterone enanthate 200-mg intramuscular/week for 12 months as a male contraceptive.[99] In the WHO male contraception study, after starting testosterone injections, there were increases in body weight, hemoglobin, and testosterone, and decreases in testicular volume, LH, and FSH. The values returned to baseline in the recovery period, lasting greater than one year. However, significant is the study finding the increase in body weight reverted to normal after testosterone cessation.

In 1992, Forbes et al. published a study describing the sequence of changes in body composition induced by testosterone and reversal of changes after drug cessation.[100] Subjects received testosterone enanthate weekly for twelve weeks and were than followed-up for a period after testosterone cessation. At the end of the treatment period, the average increment in LBM was 7.5 kg, body fat lost was 3.4 kg, and the average increment in body weight was 4.1 kg. Upon testosterone discontinuation, LBM progressively declined at a rate that suggests that half of the maximum increment was lost in about 2 months. There was no measurement of serum hormones.

In 2004, after years of published studies reporting on the positive benefits of AAS administration but with no follow-up for the period of hypogonadism after AAS cessation a

randomized controlled study reported on the body composition changes during administration and after a twelve-week follow-up period after AAS cessation.[101] The study found that the positive body composition changes in lean body mass, muscle area, and strength produced by the androgen in the study had completely disappeared twelve weeks after AAS cessation. This was due to the state of hypogonadism induced by the administration of androgens, androgen induced hypogonadism (AIH). This is proof that the thousands of individuals placed on AAS will lose any benefits upon AAS cessation but also run the risk of further adverse effects dependent on the duration and severity of AIH.

The induction of androgen deficiency by administration of a GnRH agonist is associated with adverse body composition changes. These changes in adiposity and fat-free mass are similar to trends seen in men with modest to moderate hypogonadism. In a series of elegant studies, Mauras et al. have demonstrated that lowering of serum testosterone concentrations in healthy, young men is associated with a marked decrease in measures of whole body protein anabolism, decreased strength, decreased fat oxidation, and increased adiposity.[102] Using dual-energy X-ray analysis (DEXA), there was a 2.1-kg reduction in fat-free mass and a 1.1-kg increase in fat mass, without a significant change in weight within ten weeks.

Kvorning et al. affirmed these results in healthy, young men in a twelve-week study studying the effects of induced hypogonadism on strength training.[103] The study demonstrates that suppression of endogenous testosterone production attenuates the increase in lean mass, increases storage of fat (1.4-kg), and abolishes the increase in muscle strength during strength training in normal young men. The study conclusion is that endogenous testosterone is of paramount importance for the muscular adaptation to strength training.

The use of induced hypogonadism for androgen deprivation therapy in prostate cancer produces similar changes in body composition. GnRH agonists increase weight and percentage fat body mass and decrease percentage lean body mass and muscle size in men with nonmetastatic prostate cancer. Increased fatness resulted primarily from accumulation of subcutaneous rather than intraabdominal adipose tissue.[104] Induced hypogonadism in prostate cancer patients found that fat mass increased 1.7-kg, whereas lean body mass decreased 1.7-kg.[105]

The conclusion from induced hypogonadism studies by the use of AAS or GnRH analogues whether in healthy men or those with prostate cancer is the loss of muscle mass, decreased muscle strength, and increased adiposity. The results from AAS or GnRH induced hypogonadism are qualitatively and quantitatively alike. AAS administration in clinical studies to effect positive body composition changes, muscle mass and muscle strength, disappear after AAS cessation due to the period of induced hypogonadism. The anabolic effects will be lost after AAS cessation with the additional problems of hypogonadism now facing the patient. Yet, thousands of ill, not healthy, individuals, in clinical study investigations receive AAS administration for this very purpose. The failure to account for the body composition changes after AAS cessation (AIH) is flawed scientific methodology at best and undoubtedly, the use of questionable research practices.

Psychiatric

With the support of the Swedish National Institute of Health, a national information service began in 1993 aiming to capture the use of doping agents in the public. It was organized as a telephone service, called the Anti-Doping Hot-Line, managed by trained nurses cooperating with clinical pharmacologists. The most commonly used anabolic steroids were testosterone, nandrolone-decanoate, methandienone, and stanozolol. Six of the ten most commonly reported adverse reactions were of a psychological nature, including aggressiveness, depression, anxiousness, potency problems (libido), sleep disorders, and mood disturbances.[106]

Boyadjiev describes a case report of AIH with acute aggressive and destructive behavior and found to meet the Diagnostic and Statistical Manual of Mental Disorders-IV ed. (DSM-IV) criteria for Borderline personality disorder.[107] On admission to the hospital, the clinical profile of the patient showed extremely low levels of serum testosterone and azoospermia that continued for ten months after AAS cessation.

The Federal and State government have taken special notice for the period after AAS cessation, particularly the adverse effects of clinical depression, suicidal ideation, and suicide. The Government Reform Committee Hearing, United States House of Representatives, held a hearing, on March 17, 2005.[108] The hearing was entitled "Restoring Faith in America's Pastime: Evaluating Major League Baseball's Efforts to Eradicate Steroid Use." The hearing was the first in a series of hearings regarding steroid use in professional sports. The committee received testimony from Mr. Raymond and Dr. Denise Garibaldi, parents of former USC baseball player, Rob Garibaldi, who committed suicide after steroid use at the age of 24; and from Plano, Texas Mr. Donald Hooton, Director, Chairman, and President of Taylor Hooton Foundation, and father of high school baseball player, Taylor Hooton, who committed suicide after steroid use at the age of seventeen.

Shortly thereafter Texas HB 3563, "Use Of Anabolic Steroids By Public School Students," was passed and signed into law June 18, 2005. Of particular importance is the bill analysis citing the problem of "clinical depression when steroid use is stopped."[109] After the cessation of anabolic steroids (AAS), a period of hypogonadism ensues. The name for the condition during this period is androgen, anabolic steroid induced hypogonadism (AIH).

Hypogonadism is an important cause of mood disturbances. Hypogonadal men are more depressed, angered, fatigued, and confused than infertile, treated eugonadal, or normal men. Studies show positive relationships between androgen levels and mood and well-being. Circulating concentrations of testosterone are correlated with mood indices in older men and in men with a number of chronic illnesses. In general, androgens improved positive aspects of mood and reduce negative aspects of mood such as irritability in young, hypogonadal men.[110] In one cross-sectional study of community dwelling, older men, the men who were depressed had the lowest testosterone levels.

These psychological disturbances are present in studies using the induced hypogonadism model as well. A study on induced hypogonadism in healthy young men suggests that short-term hypogonadism is sufficient to precipitate depressive symptoms in a small minority of younger

men. The predictors of this susceptibility remain to be determined.[111] Treatment for prostate cancer frequently includes androgen deprivation therapy (ADT). Reports of depressive symptoms arising during ADT are emerging, however, the association is unclear, and other contributing factors might be important.[112]

Hypogonadism is an important cause of sexual dysfunction.[113] Sexual function in men is a complex process that includes central mechanisms for regulation of sexual desire and arousability, and local mechanisms for penile tumescence, orgasm, and ejaculation. Hypogonadal men have decreased frequency of sexual thoughts, lower overall sexual activity scores, and lower frequency and duration of the episodes of nocturnal penile tumescence. Nocturnal penile tumescence (NPT), the occurrence of spontaneous erections during rapid eye movement (REM) sleep, is relevant. NPT is clearly impaired in hypogonadal men, and restored to normal with testosterone replacement.

The importance of androgens in establishing and maintaining sexual function in males of most species is well recognized. Most controlled studies of testosterone replacement in hypogonadal men have used a period of withdrawal as a baseline, followed by the administration of testosterone and placebo, using a double-blind crossover design. Such studies consistently show a reduction in the level of sexual interest during testosterone withdrawal consistent with testosterone being necessary for normal levels of sexual interest (and arousability).

Bagatell et al. used induced hypogonadism in healthy-young med to study sexual function.[114] Induced hypogonadism produced clinically and statistically significant decreases in the frequency of sexual desire, sexual fantasies, and intercourse. These men also showed a strong trend towards decreased spontaneous erections and a significant decrease in the frequency of masturbation. There was a trend toward increased aggression while hypogonadal, but this did not reach statistical significance.

Hypogonadism is an important cause of decreased cognitive abilities (memory and concentration). Barrett-Conner et al. found positive associations between total and bioavailable testosterone levels, and global cognitive functioning and mental control, but not with visuospatial skills. Hypogonadal men performed worse on tests of verbal fluency than eugonadal men, and showed improvement after testosterone replacement.[115] A study examining the effects of sex steroids on cognitive functioning found induced decreased serum testosterone levels adversely affects verbal memory in normal young men. These results suggest that short-term changes in sex steroid levels have effects on cognitive function in healthy young men.[116]

The possible role of gonadal steroids in regulating sleep and circadian rhythms in humans has received relatively little attention despite the importance of the topic to several clinical syndromes. Results from induced hypogonadism revealed significant decreases in the percentage and time of stage 4 sleep in the hypogonadal state.[117] These results indicate that testosterone has relatively specific and discrete effects on sleep in men. In addition, studies describe an association between fatigue (diminished energy) and hypogonadism.[118]

Cardiovascular

Because adiposity is associated with heightened cardiovascular risk, these data suggest that hypogonadism may have important implications with regard to health. In addition to its role in the modulation of body composition, testosterone may be involved directly in the regulation of vascular tone.

Cardiovascular disease is the major cause of death among men worldwide. Sex hormones appear to play a pivotal role in determining cardiovascular risk. In cross-sectional studies, there is a direct correlation between circulating testosterone concentrations and tissue plasminogen activator activity and an inverse relationship between testosterone and plasminogen activator inhibitor-1 activity, fibrinogen, and other prothrombotic factors, suggesting an antithrombotic effect of testosterone.[119]

Testosterone has been shown to dilate coronary, aortic, and brachial vasculature by both endothelial-dependent and independent mechanisms.[120] These observations suggest that testosterone may be an important regulator of vascular compliance in large and medium-sized arteries. Increased vascular stiffness has important hemodynamic consequences, and evidence is mounting that vascular stiffness is an independent marker of cardiovascular risk.[121] Arterial compliance or stiffness is a possible modifiable risk factor for cardiovascular disease. This supports the view that physiological levels of androgens may protect the vasculature.

Published literature demonstrates an association between lower androgenicity and increased cardiovascular risk in men.[122] Most cross-sectional studies have repetitively found an association between hypotestosteronemia and cardiovascular morbidity. Observational studies show that blood testosterone concentrations are consistently lower among men with cardiovascular disease, suggesting a possible preventive role for testosterone therapy.

Androgen deprivation therapy for males results in a hypogonadal state that may have important effects on the vasculature. Induced hypogonadism markedly increases fat mass in men, raising the question of an increase in cardiovascular risk. Smith et al. studying the effects of ADT over a six-month period on prostate cancer patients found adverse body compositional changes of an increased fat mass, rising insulin concentrations, and a rise in the augmentation of central arterial pressure, suggesting large artery stiffening.[123] In a prospective 12-week study, short-term treatment with GnRH agonists to produce induced hypogonadism significantly increased fat mass and decreased insulin sensitivity in men with prostate cancer.[124]

Dockery et al. in a series of clinical studies investigated the loss of androgen in men and metabolic and hemodynamic factors related to cardiovascular disease.[125] Induced hypogonadism leads to an increase in aortic stiffness, a reduction in central arterial compliance, increase in serum insulin levels, and may therefore adversely affect cardiovascular risk. The known association between lower androgenicity and increased cardiovascular risk in men might be explained by altered vascular stiffness.

These adverse hemodynamic and metabolic effects suggest that induced hypogonadism may increase the risk of diabetes mellitus and cardiovascular disease in older men.[126] Induced hypogonadism leads to an increase in aortic stiffness, a reduction in central arterial compliance, increase in serum insulin levels, and may therefore adversely affect cardiovascular risk. Of

importance is if induced hypogonadism adversely affects cardiovascular risk does this translate into significant cardiovascular morbidity and mortality. In 2007, a published study concludes the use of GnRH induced hypogonadism in elderly men is associated with earlier onset of fatal myocardial infarctions.[127]

Androgens in general and testosterone in particular may have some protective effects on the cardiovascular system through their metabolic and direct effects upon human vasculature.[128] The conclusion from both hypogonadism and induced hypogonadism studies is an increase risk of cardiovascular morbidity and mortality. Investigators studying AAS use are in the expectation they are aware of the relationship between hypogonadism and cardiovascular risk factors whether those studies are definitive or not. At the very minimum, the reporting of adverse cardiovascular events during AAS administration and assuredly after AAS administration cessation when hypogonadism is most likely would alert investigators to monitor serum testosterone levels.

FAILURE TO RECOGNIZE AND ACCOUNT FOR AIH LEADS TO BIASED RESULTS AND ADVERSE CONSEQUENCES

Investigators and editors developed the CONSORT (Consolidated Standards of Reporting Trials) statement to help authors improve reporting by using a checklist and flow diagram.[129] CONSORT Item 19, Results, states the reporting of all important adverse events or side effects in each intervention group. CONSORT Item 20-22, Comment, includes proper interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes, generalizability (external validity) of the trial findings, and general interpretation of the results in the context of current evidence. None of the authors in the above referenced studies adhered to these standards.

To comprehend the results of a randomized controlled trial (RCT), readers must understand its design, conduct, analysis, and interpretation. To assess the strengths and limitations of a RCT, readers need and deserve to know the quality of its methods. A RCT is less susceptible to bias than other study designs for assessing therapeutic interventions. However, just because a study is randomized does not mean it is unbiased. There are several important potential sources of bias in RCTs. These include missing data, competing interests, early stopping, and adverse events.[130] The reporting of RCTs is still inadequate. Inadequate reporting makes the interpretation of RCT results difficult if not impossible. Moreover, inadequate reporting borders on unethical practice when biased results receive false credibility.

The definition of bias, systematic error, is any process or effect at any stage of a study from its design to its execution to the application of information from the study that produces results or conclusions that differ systematically from the truth. Bias is the systematic distortion of the estimated intervention effect away from the "truth," caused by inadequacies in the design, conduct, or analysis of a trial. When assessing bias, it is important to consider its magnitude as well as its direction. Elimination or reduction of bias is only by proper study design and execution and not by increasing sample size.

Questions requiring answers on the validity of study results include whether intervention and control groups begin the study with a similar prognosis, whether intervention and control groups retain a similar prognosis after the study started, and was follow-up complete.[131] Hypogonadism has an adverse effect upon the primary outcomes of the study. In these studies, the intervention, AAS, causes a change in the prognosis in the treatment group. This introduces bias, making the conclusions invalid. Anabolic steroid research focuses only on the period of AAS administration, while at the same time dismissing and ignoring the period after AAS cessation that affect the validity of their conclusions. Clinical application of published study results is dependent upon sound research design, if not undue harm is a possibility.

Clinical studies describe AAS prescribing for elderly, chronic kidney disease (hemodialysis), HIV+ males, chronic obstructive pulmonary disease, and rheumatological disorders on long-term glucocorticoids. AAS treatment for these conditions is towards disease-associated morbidity, decreased muscle mass and decreased muscle strength, not treatment for the underlying disease cause. The treatment for these conditions is of a limited duration. In addition, adverse effects necessitate and require the discontinuation of these drugs.

In these studies, the intervention, AAS, causes a change in the prognosis in the treatment group. This introduces bias, making the conclusions invalid. Biased research results open the door for harm to patients extending far beyond those subjects involved in the clinical trial. These results may lead to erroneous conclusions about the safety or the efficacy of drugs. Researchers working on the next generation of research, creating a domino effect of error, will also use them. Once disseminated in the market, end user physicians and patients will pay the price for bad science in dollars, poor outcomes, and adverse events.[132]

Hypogonadism is associated with adverse health outcomes affecting morbidity and mortality that require life-long treatment. Synthetic anabolic steroids in the doses used in clinical research studies cause hypogonadism after their cessation. The use of fatally flawed methodology in AAS research by well-established academic institutions and researchers is indicative of an arrogance and disdain for others.

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HENRY K. BEECHER: ECHO & REVERBERATIONS

“Medicine is, at its center, a moral enterprise grounded in a covenant of trust. This covenant obliges physicians . . . to use their competence in the patient’s best interests.”[133]

An active conscience, like competence, is a virtue expected in any profession for, by their nature, professions should involve a measure of altruism in serving the public good.[134]

"I am aware that these are troubling charges. They have grown out of troubling practices. They can be documented, as I propose to do, by examples from leading medical schools, university hospitals, private hospitals . . . The basis for the charges is broad."[135] "These examples . . . are recorded to call attention to a variety of ethical problems found in experimental medicine, for it is hoped that calling attention to them will help to correct abuses present. . . . [i]t is evident that in many of the examples presented, the investigators have risked the health or the life of their subjects. No attempt has been made to present the "worst" possible examples; rather, the aim has been to show the variety of problems encountered."[136] Investigators who intentionally allow bias or error to infect their work are practicing scientific misconduct. That includes such things as designing studies to ensure a desired result, making statements not justified by the evidence, publishing only part of the evidence, suppression of research findings, and outright fraud with fabrication of evidence.”[137]

Historically, the medical profession demonstrates not to have the ability to police itself.[138] Physicians violate ethical, medical, and legal frameworks to guide and restrict their behavior in the protection of human rights. The ethical, medical, and legal framework of human research protections repeatedly demonstrates to be wholly inadequate. This is the history of the past, current, and will undoubtedly be that of the future.

Physician oaths as a means of personal self-regulation have no effect on physician behavior. Although physicians have taken oaths, often expressed in the form of written codes, since before 2000 B.C., these codes have not hindered violations of patient rights. Physicians have formed medical organizations to promote medical responsibility and there is no evidence to suggest that these organizations have regulated physician behavior or protected the rights of subjects to free and informed consent.

The medical community claims it has gotten its own house in order with the emergence of evidence-based medicine (EBM).[139] However, EBM represents a reaction to the failure of generalist decision makers to appreciate the power and limitations of the scientific literature.

Almost universally medical treatments fall short of the ideal imagined by the proponents of EBM.[140] In desperate efforts to bring about the protection of human research subjects, after decades of documentation of abuses in human research, legislation of regulations and laws, amended repeatedly to improve protections originally articulated in the Nuremberg Code, also fail to change physician behavior.

In 1966, anesthesiologist Dr. Henry K. Beecher wrote in the New England Journal of Medicine, "Ethics and Clinical Research," describing 22 examples of research studies with controversial ethics that had been conducted by reputable researchers and published in major journals.[141] Beecher provides estimates and concludes, "[u]nethical or questionably ethical procedures are not uncommon."

Forty plus years later, one might expect that ethical violations would be rare, that physician-researchers would adhere to the highest of ethical standards, the Nuremberg Code principles would be the commonplace guidepost, and an individual's health and welfare is of the utmost priority. Sadly, the polar opposite appears to be the case and rather than advance the boundaries of scientific knowledge and medical treatments, the only increase is in the financial statement bottom line of physician-investigators and the companies to which they ally themselves.

The Nuremberg Code's first principle, "The voluntary consent of the human subject is absolutely essential," is an absolute upon which the others rest.[142] Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment.[143]

The words written by Henry K. Beecher are equally appropriate for the research community today. "Human experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them. Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as a direct result of experiments described here."[144]

Science and ethics do not conflict; valid science is an ethical requirement. Without validity, the research cannot generate the intended knowledge, cannot produce any benefit, and cannot justify exposing subjects to burdens or risks.[145] Unless research generates reliable and valid data that is interpretable and usable by the specified beneficiaries of the research, it will have no social value, and expose participants to risks for no benefits.[146]

The design of a research study must be so that the results will be useful in the context of the health problem.[147] The selection of interventions should be to ensure that the design is useful in identifying effective or appropriate interventions; implementing socially, culturally, and economically appropriate changes in the health-care system; or providing a reliable foundation for conducting subsequent research. The selection of interventions is to ensure that the design

will realize social value and that the data are generalizable to the host community. [148]"Invalid research is unethical because it is a waste of resources as well: of the investigator, the funding agency, and anyone who attends to the research."[149]

CIOMS guidelines succinctly state: "Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose."[150] To be ethical, the conducting of valuable research must be in a methodologically rigorous manner.[151] For a clinical research protocol to be ethical, the methods must be valid and practically feasible. The research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan. Of course, the development and approval of a valid method is of little use if the research is conducted in a sloppy or inaccurate manner; careless research that produces uninterpretable data is not just a waste of time and resources, it is unethical.

Physicist Richard Feynman communicating the basic principles of science in his 1974 commencement address at the California Institute of Technology:[152]

> [There is an] idea that we all hope you have learned in studying science in school—we never explicitly say what this is, but just hope that you catch on by all the examples of scientific investigation. It's a kind of scientific integrity, a principle of scientific thought that corresponds to a kind of utter honesty—a kind of leaning over backwards. For example, if you're doing an experiment, you should report everything that you think might make it invalid—not only what you think is right about it; other causes that could possibly explain your results; and things you thought of that you've eliminated by some other experiment, and how they worked—to make sure the other fellow can tell they have been eliminated.
>
> Details that could throw doubt on your interpretation must be given, if you know them. You must do the best you can—if you know anything at all wrong, or possibly wrong—to explain it. If you make a theory, for example, and advertise it, or put it out, then you must also put down all the facts that disagree with it, as well as those that agree with it. In summary, the idea is to try to give all the information to help others to judge the value of your contribution, not just the information that leads to judgment in one particular direction or another.

In men, therapy with testosterone and its analogs has been shown to increase muscle mass, decrease fat mass, and improve muscle strength. Well-controlled trials of testosterone supplementation in healthy young men and older men have demonstrated that muscle mass and strength increase with a linear dose-response relationship; an appreciable hypertrophic response occurs within the physiologic range of circulating testosterone levels. [153]

Because of the effects of testosterone in enhancing lean body mass (LBM), muscle strength, and decreased adiposity studies investigate the possible role for testosterone or anabolic steroids (AAS) in catabolic states. Anabolic steroids other than testosterone have received particular attention with regard to improving body composition not only in normal populations but also in those with chronic illness. These include sarcopenia (loss of muscle mass and muscle strength in ageing), chronic renal failure (hemodialysis), chronic obstructive lung disease (COPD), HIV+, osteoporosis, and long-term glucocorticoid administration. These studies are indicative of the developing trend in using aggressive pharmacological therapy with anabolic steroids to reverse declines in lean body mass and muscle strength.

The main therapeutic goals of AAS administration is to effect positive body composition changes. All compounds classified as androgens or anabolic-androgenic steroids suppress endogenous testosterone production as well as gonadotropin release, the modulators of body composition changes. AAS, licit and illicit, induce a state of hypogonadism after their cessation. No studies exist which describe the return of normal function and the extent of hypogonadism in subjects after androgen cessation. Published studies utilizing androgen or androgenic anabolic steroids (AAS) therapy have not addressed the effects of hypogonadism after androgen cessation. There is no doubt that the researchers are well aware of anabolic steroid induced hypogonadism (ASIH) having been described in the published literature for over fifty years.

Studies done on these patients demonstrating the positive body composition changes with AAS administration fail to include the follow-up period after AAS cessation. The published literature conclusively demonstrates the adverse effects of ASIH are the same seen for hypogonadism and even may be much worse. These effects include those that directly affect the primary outcomes of the above referenced study. Upon discontinuation of AAS, these patients would develop anabolic steroid induced hypogonadism (ASIH), which negates the positive body composition changes and potentially leave them in a state of health worse than when first prescribed AAS. The most significant concern is marginally healthy individuals placed on AAS for this goal may be placing themselves at an even greater morbidity and mortality risk upon AAS cessation.

It is inarguable that in medicine, an adverse effect is a harmful and undesired effect resulting from a medication or other intervention. An adverse effect or side effect (when judged secondary to a main or therapeutic effect) may result from an unsuitable or incorrect dosage or procedure (which could be due to medical error). Adverse effects are sometimes "iatrogenic" because they are physician/treatment generated. Some adverse effects only occur only when starting, increasing, or discontinuing a treatment. Adverse effects may cause medical complications of a disease or procedure and negatively affect its prognosis. They may also lead to non-compliance with a treatment regimen.

Indications of a harmful outcome is usually by some result such as morbidity, mortality, body weight alteration, enzyme levels, loss of function, or a pathological change detected at the microscopic, macroscopic, or physiological level. Other indications include symptoms reported by a patient. Adverse effects may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other disease.

These studies are inexcusable for the failure to include the effects of hypogonadism after AAS cessation. Effects that had they been included would surely negate the significant positive body composition changes found and the proposed and hypothetical benefit of AAS treatment. Extraordinarily unethical and unsound scientific methodology in clinical trials places a countless number of vulnerable individuals in harms way.

These studies violate human research protections as provided by 45 C.F.R. § 46, Subpart A, Protection of Human Subjects. The violations include the failure to use a sound research design, failure to use sound research methodology, and not providing a fully informed consent.

This includes the failures to use sound research design and sound research methodology, required by DHHS regulations at 45 C.F.R. § 46.111, that does not unnecessarily expose subjects to risk, failure to ensure that the risks to the subjects are reasonable in relation to the anticipated benefits, and failure to ensure that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

A critical part of any study involving AAS will include by necessity the measurement of sex hormones, which are the gonadotropins and testosterone. Not to provide for the monitoring, measurement, of the sex hormones during the study is, in itself, a violation of 45 CFR 46.111.

Hypogonadism is a class of diseases with the common laboratory finding of a decrease in testosterone or spermatogenesis. The research design and research methodology did not make provisions for data monitoring of concern to the safety of the patients, specifically for testosterone levels during, on conclusion, and following AAS administration, thus failing to monitor for a possible hypogonadal state in the subjects. These risks include but are not limited to adverse body composition changes, increase in cardiovascular risk, and psychiatric side effects that include depression and mood disturbances.

The use of sound research methodology depends upon the testing for biochemical markers of hypogonadism. AAS effect on HPTA physiology is in peer-reviewed literature for over fifty years. All published literature demonstrates HPTA suppression with AAS administration. The available published literature in existence does show ASIH, in fact, one-hundred percent of the time.

The research design did not take into consideration that the use of AAS causes a disruption of the hypothalamic-pituitary-testicular axis (HPTA), resulting in a state of induced hypogonadism. The disruption of the HPTA results in a state of hypogonadism in the subject that continues after AAS cessation. Hypogonadism has an adverse effect upon the primary outcomes of the study. Considering the AAS dosage administered in these studies, there is no question that subjects were left hypogonadal post therapy. The intervention causes a change in the prognosis in the treatment group. This introduces bias, thus making the conclusions invalid. The investigators responsibility is not to ignore and dismiss data that might alter the risk/benefit results but to include such data and more importantly, protect the safety of the patient.

The informed consent process for the research failed to include the elements required by DHHS regulations at 45 C.F.R. § 46.116. Informed consent deficiencies includes the failure to

document accurately the duration of subject's participation, failure to document the foreseeable risks or discomforts to the subject, failure to document risks greater than minimal risk that include failure to explain medical treatments for injury, failure to document risks of particular treatment to the subject, failure to document treatment costs for injury from treatment, failure to document consequences of withdrawal from research, and failure to provide subjects with information and findings that relate to the subject's willingness to continue participation.

Regarding informed consent, Beecher writes, "The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and unless all hazards are made clear. If these are not known this, too, should be stated." Without consideration in the research design, research methodology, and data monitoring for hypogonadism during and after AAS administration, it is not possible to give a fully informed consent upon which one can make a decision to participate in the clinical trial.

None of the papers published since 1992 referenced, cited, discussed, or mentioned the early papers describing the adverse event, ASIH, after AAS cessation. Countless studies have reported on the positive body composition changes with AAS administration for many medical conditions. A fatal methodological flaw in study design is responsible for the different effects before 1992 (adverse) and after 1992 (positive), failure to account for homeostasis. Each of these studies examined the effects of AAS and reported their results. In papers 1992 and before descriptions and reporting included the follow-up period after AAS cessation. These studies included consideration for HPTA normalization, the follow-up period after AAS cessation. Beginning in 1992 there was no examination and reporting of the effects of AAS cessation during a follow-up period. Each of these studies suffered from a serious methodological flaw in their study design, not commented upon or reported.

It is hard if not impossible to comprehend or fathom on how a known side effect to occur in one-hundred percent of individuals taking AAS, licit or illicit, could be ignored if it was not purposeful. The following pages describe how government ignorance, the pharmaceutical industry, and medical research community failed to acknowledge known AAS adverse effects. Reasons for this failure are the direct and deliberate intent of each of these parties to uphold their responsibility to act according to their own charters or missions. This collective failure has put the public health and welfare in harms way. But most of all this is a failure of individuals, not corporations or entities, in the form of physicians and others who fail to protect that we hold most dear to the essence of man, goodness.

While Henry K. Beecher's publication in 1966 covers many areas of medicine, the increase in medical research easily produces countless breaches of ethical conduct in a single area of research, in this case anabolic steroids (AAS). The number of human research subjects affected alone by unethical and unsound practices in AAS research numbers into the thousands. Those similarly affected by physicians that have implemented these course of treatments in their own patients assuredly numbers in the ten thousands if not hundreds of thousands.

There is a strong argument that physicians have historically shown little inclination to police themselves voluntarily. The ease with which physicians breach this framework is proof the system of protections has completely broken down. No amount of ethical training, codes,

declarations, and regulations serves to minimize or prevent human research protection violations. The time is long past for strengthening empty words with criminal sanctions against those that practice medicine and research in such a reckless disregard for human life.

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HUMAN IMMUNODEFICIENCY VIRUS (HIV)

By definition, an individual with a diagnosis of being HIV+ is someone who has a life threatening disease, which at best is a chronic life-long illness, and whose medical care is critical in maintaining optimal health. Their healthcare is constant and unremitting, consisting of a daily routine of multiple medications, a proper balanced and nutritional diet, avoidance of opportunistic infection, and a heightened awareness for this balance. Any threat that jeopardizes this delicate balance is one that may immediately place their life in imminent danger.

Published studies of growth hormone and anabolic steroid treatments of wasting syndrome have not included prolonged follow-up and survival information. There are no studies finding improved survival associated with hormone-based treatments of wasting syndrome. To date, prescription of anabolic steroids or growth hormone is not associated with improved survival. In addition, the studies in the published literature do not account for anabolic steroid induced hypogonadism (ASIH). Barring medical intervention to minimize or prevent ASIH after AAS cessation, there is no empirical evidence for the use of AAS treatment to produce positive body composition changes, and the use of anabolic steroids to promote positive body composition changes is not justified, dangerous, and abuse. Yet, as the following illustrates these studies populate the peer-reviewed literature.

The human immunodeficiency virus (HIV) was unknown until the early 1980's but has infected millions of persons since that time, resulting in a worldwide pandemic. The result of HIV infection is relentless destruction of the immune system leading to onset of the acquired immunodeficiency syndrome (AIDS). The AIDS epidemic has already resulted in the deaths of over half its victims. All HIV-infected persons are at risk for illness and death from opportunistic infectious and neoplastic complications because of the inevitable manifestations of AIDS.[154]

Although the HIV infection rate in the United States peaked in the late 1980's and has declined since, the reservoir of HIV-infected persons developing AIDS and requiring therapy continued to increase through the 1990's and into the 21st century.[155] Costs for detection, diagnosis, and treatment are considerable and increase further with development of effective therapies for persons with complications of HIV infection and their subsequent longer survival. In the 1990’s in the U.S., the average cost for medical care of an HIV-infected patient was double the average income for half of all such patients.[156] A proper understanding of AIDS

issues, including the nature and treatment of HIV, should precede decisions regarding allocation of health care resources and control measures.[157]

Human immunodeficiency virus (HIV) and its subtypes are retroviruses, and they are the etiologic agents of AIDS. Human retroviruses were unknown until the 1980's. HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses that are characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods following infection before manifestations of illness become apparent.[158]

Primary HIV infection, also known as acute retroviral syndrome, may produce a mild and self-limited disease in 50% to 90% of persons infected with HIV, regardless of the mode of transmission. The time from mucosal infection to viremia is about 4 to 11 days. The time from exposure to development of symptoms averages 2 to 6 weeks. The symptoms may persist for 1 to 2 weeks, after which symptoms subside over 1 to 2 months. The symptoms of acute HIV infection resemble a flu-like or an infectious mononucleosis-like syndrome. Primary HIV infection is not life threatening.[159]

The period of clinical latency with HIV infection can be variable, from as short as 18 months to over 15 years. This latent period lasts, on average, from eight to ten years.[160] About 10% of persons will rapidly progress to AIDS in 2 to 3 years following HIV infection, while about 10% have not progressed to AIDS even after 10 years.[161] It is clear that the longer an individual is infected, the more likely the development of illness and subsequent death will be. Thus, HIV infection does not follow the pattern of more traditional viral diseases in which the risk of serious illness or death decreases with time. There has been no study to date that shows a failure of HIV-infected persons to evolve to clinical AIDS over time, though the speed at which this evolution occurs may vary, and a small number of HIV-infected persons will not progress to AIDS for many years.[162] The stage of clinical AIDS that is reached years after initial infection is marked by the appearance of one or more of the typical opportunistic infections or neoplasms diagnostic of AIDS by definitional criteria.

Persons with HIV infection can be categorized as typical progressors, rapid progressors, and nonprogressors toward AIDS. The typical progressors average 8 to 10 years of latent HIV infection before the appearance of clinical AIDS. About 10% of HIV-infected persons rapidly progress to AIDS in only 2 to 3 years following initial infection. About 10% of persons infected with HIV-1 are nonprogressors, or long-survivors, who do not demonstrate a significant and progressive decline in immune function over more than 10 years. They do not appear to progress to AIDS in a manner similar to the majority of HIV-infected persons.[163]

Though most HIV infections follow a standard progression, previously asymptomatic persons may suddenly die from an overwhelming opportunistic infection, while persons with clinically defined AIDS may survive for years. Progression to AIDS in persons with HIV infection does not appear to be modified by gender, race, or pregnancy. Progression to AIDS does appear to be accelerated in persons who are older or who smoke.[164] A younger age at seroconversion, initial diagnosis of Kaposi's sarcoma, and infection at a more recent calendar time are all associated with slower progression.[165] Persons who manifest symptomatic acute HIV infection have a faster progression to clinical AIDS.[166] Constitutional symptoms, reported by

more than 50% of people with advanced HIV disease, often significantly compromise both physical functioning and quality of life.[167] The most common constitutional symptoms include weight loss, fatigue, fever, and sweats.

Weight loss occurs frequently in HIV-infected patients, particularly those with AIDS.[168] HIV wasting syndrome is a progressive, involuntary weight loss is a common accompaniment to HIV infection. Wasting has been a prominent feature of HIV infection since its emergence. In the earlier stages of the epidemic, it was associated with extremely high morbidity and mortality,[169] and it has been an AIDS-defining condition since 1993.[170] The progression of HIV infection may play a role in the appearance of wasting syndrome, since the degree of weight loss correlates with increasing HIV-1 RNA levels and with decreasing CD4 lymphocyte counts.[171]

The incidence of AIDS-defining opportunistic illnesses has markedly decreased since the introduction of highly active antiretroviral therapy (HAART) in the United States and elsewhere.[172] The incidence of wasting syndrome has decreased by approximately 50%.[173] It is still strongly related to the risk of disease progression and death, even in the era of HAART.[174] Of course, wasting remains a devastating problem in most of the world affected by AIDS, where such therapy is not readily available.[175]

HIV wasting syndrome is a common AIDS defining diagnosis in the United States, with an estimated lifetime frequency of 70% to 90% among AIDS patients who receive no antiretroviral therapy.[176] It is defined by the Centers for Disease Control and Prevention as an involuntary loss of more than 10% of baseline body weight in conjunction with fever, weakness, or diarrhea for more than 30 days. However, less stringent definitions, such as loss of 5% to 10% of ideal body weight, are widely employed in clinical practice.[177] In the U.S., HIV wasting syndrome alone as an indicator disease accounts for 7% of all newly reported AIDS cases, and is reported along with additional indicator diseases in another 10% of cases. In the U.S., persons with HIV wasting syndrome are more likely to be female, black, or Hispanic, and have a risk factor other than homosexuality/bisexuality.[178]

There are persons with AIDS who do not have a concurrent illness or condition other than HIV infection that explains a weight loss of >10% of baseline body weight plus either chronic diarrhea or chronic weakness and fever, which are the CDC criteria for HIV wasting syndrome that satisfy definitional criteria for a diagnosis of AIDS.[179] This wasting syndrome primarily results from loss of lean body mass, while body fat stores are preserved.[180]

Mechanisms of HIV wasting are complex and include diminished or inadequate nutrient intake, excessive nutrient loss, and metabolic dysregulation.[181] Decreased oral intake of food is also a very important etiology for weight loss in HIV infection and highlights the need for good nutrition. Poor diet from lack of sufficient care or economic resources certainly plays a role, as well as malabsorption from concomitant AIDS-associated infections or neoplasms, particularly those affecting the gastrointestinal tract.

Despite the development of improved therapies for HIV infection and a dramatic reduction in mortality and wasting,[182] weight loss continues to be a problem among infected persons.[183] Several causative factors probably contribute to the development of wasting

syndrome. These can include hypermetabolic or altered metabolic states, production of cytokines such as tumor necrosis factor, interferons, and interleukin because of macrophage infection by HIV, and endocrine dysfunction.[184]

A variety of therapies has been utilized to counteract wasting syndrome. These include the use of megestrol acetate (Megace) as an appetite stimulant, thalidomide as a cytokine inhibitor, recombinant human growth hormone, and anabolic agents.[185] Clinical trials have studied strength training and anabolic medications for the treatment of AIDS wasting. Strength training alone is also effective for restoring weight and lean body mass in HIV wasting.[186]

The rationale for AAS therapy is that body weight loss is an important terminal determinant of survival with death estimated to occur when lean body mass reaches 66% of ideal.[187] This leads to the hypothesis that androgens may delay death by increasing appetite and/or body weight. Several randomized placebo-controlled studies of androgen therapy in HIV-positive men with AIDS wasting have reported increased lean and decreased fat mass due to testosterone with additive effects from resistance training but inconsistent improvement in quality of life. Among HIV-positive men without wasting, androgen induced changes in body composition are less and unaccompanied by any improvement in quality of life.[188]

In 2003, Dworkin and Williamson reported on, "AIDS wasting syndrome: trends, influence on opportunistic infections, and survival."[189] The authors examined data from a large cohort of HIV-infected persons to demonstrate recent trends in wasting syndrome, to examine the influence of wasting syndrome on the incidence of other opportunistic illnesses, and to explore if any of the commonly prescribed treatments for wasting are associated with improved survival.

The incidence of wasting declined during 1992 through 1999, with the most marked rate of decline occurring after 1995. Improved survival after the diagnosis of wasting syndrome was found for the interval of 1996 through the first half of 1999 compared with 1992 through 1995. The incidence of AIDS and non-AIDS-defining illnesses was generally high at or after a diagnosis of wasting syndrome. Factors significantly associated with improved survival include having a CD4+ count of $\geq$200 cells/L during the interval of the wasting syndrome diagnosis and antiretroviral therapy with two or more drugs at or after the diagnosis of wasting syndrome, improved survival was not associated with growth hormone or anabolic steroids.

Lean body mass has been shown to increase with the use of recombinant human growth hormone.[190] In the presence of hypogonadism, testosterone clearly improves weight and lean body mass.[191] Since anabolic agents, anabolic steroids and growth hormone, promote tissue building (muscle and bone) these drugs have been exhaustively studied. Most notable among the peer reviewed literature is the abundance of studies using anabolic steroids as treatments in HIV+ males for positive body composition changes. Theorized is these drugs could potentially reverse or prevent weight loss and increase lean body mass in HIV-infected patients.

Studies published use the anabolic steroids testosterone, nandrolone, oxandrolone, and oxymetholone as treatments to effect positive body composition changes in HIV+ men. In all of these studies, there is clear indication of HPTA suppression by the changes in the sex hormones,

either luteinizing hormone or testosterone or both, or clinical signs or symptomatology. As described previously, induced hypogonadism has an adverse effect upon body composition changes, decreasing lean body mass and increasing adiposity.

The Food and Drug Administration (FDA) requires manufacturers to show that their products pass tests of efficacy and safety. The FDA requires several phases of testing, as laid out in the Federal Food, Drug, and Cosmetic Act (FDCA), before allowing a drug to be sold to the public.[192] FDA approval translates into tens and hundreds of millions of dollars for the manufacturer. For each day's delay in gaining FDA approval of a drug, the manufacturer loses, on average, $1.3 million.[193] Although physicians have total regulatory freedom to supply any drug approved by the Food and Drug Administration (FDA) for any use, the FDA forbids drug companies from marketing a drug for indications other than those for which the drug has won FDA approval. This ban applies to marketing to physicians as well as to consumers, although pharmaceutical companies may "share research and journal articles with doctors that discuss unapproved uses."[194]

In addition to the obvious concerns these skewed or delayed studies raise with respect to scientific integrity, biased research results open the door for harm to patients extending far beyond those subjects involved in the clinical trial. These results may lead to erroneous conclusions about the safety or the efficacy of drugs. The erroneous data and conclusions when compared to an FDA approved drug may lead one to believe their equivalence. Researchers working on the next generation of research, creating a domino effect of error, will also use them. Once disseminated in the market, end user physicians and patients will pay the price for bad science in dollars, poor outcomes, and adverse events.[195]

Bhasin and colleagues have brought the events portrayed above to reality. In 2005, a study reported on nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone (rhGH) as active reference treatment.[196] The study was a comparison of the effectiveness of a biweekly regimen of 150 mg nandrolone and contrasted its effects against a Food and Drug Administration approved regimen of rhGH. Not surprisingly, support for the study was primarily by a grant from Organon, Inc., manufacturer of nandrolone decanoate.[197] Nandrolone decanoate (nandrolone), sold under the brand name Deca-Durabolin (Organon, Oss, The Netherlands), is an androgen that is used commonly in the HIV community.

The primary outcome variable was change from baseline to week 12 in LBM measured by dual-energy x-ray absorptiometry (DEXA). Secondary outcome variables were other changes in body composition. These include subcutaneous and intraabdominal adipose tissue volumes by magnetic resonance imaging (MRI), total body water by deuterium oxide dilution method, and bioelectrical impedance analysis (BIA) for LBM, body cell mass, fat mass, intracellular water, and extracellular water.

In this 12-week clinical trial, placebo, nandrolone (150 mg intramuscular biweekly), and rhGH (6 mg subcutaneous daily) was administered. Assessment of body composition changes, muscle performance, physical function, endurance, hormone levels, insulin sensitivity, sexual function, quality of life, and appetite were at baseline and after 12 week.

Measures of muscle performance (leg press strength, chest press strength, leg power, and fatigability), measures of physical function (400-m walk time, stair-climbing time, stair-climbing power, and time-carrying load), and measures of endurance (lactate threshold, endurance time, and VO_2 max) did not show significant treatment effects.

Perception of overall health, assessed by the Medical Outcomes Study–Short Form 30 questionnaire, improved in men treated with nandrolone than in those receiving rhGH ($P<0.05$). The percentage of subjects who responded affirmatively to items "easy to achieve an erection" and "satisfied with the sex I have" was higher in the nandrolone (24.4 and 43.9%) and rhGH (35.0 and 45.0%) groups than in the placebo (4.8 and 9.5%) group. The cachexia/anorexia scores, health care resource use, and insulin sensitivity did not significantly change in any group.

The study cites rhGH administration was associated with higher frequency of drug-related adverse effects and treatment discontinuations than nandrolone and placebo and a greater increase in extracellular water than nandrolone. The percentage of subjects experiencing a drug-related adverse event was higher in the rhGH group (47.6%) than in placebo (4.8%) or nandrolone (4.7%) groups. The adverse events include peripheral edema (four in the rhGH group), arthralgia (three in the nandrolone group, nine in the rhGH group), and carpal tunnel syndrome (four in the rhGH group). Three subjects, all in the rhGH group, discontinued treatment due to an adverse event.

What the authors do not discuss is the origin of rhGH effects and the possible treatments available. This is even more so when consideration is given that the etiology for these events is rhGH ability to retain extracellular water and treatment typically is a simple diuretic or reduction in dose. This fact is found in the study results, "In comparison with nandrolone treatment, administration of rhGH was associated with greater loss of whole-body fat mass and greater gain in extracellular water." There is a serious question as to bias that the authors attribute to these adverse events, particularly in light of the study sponsor. Regardless, the conclusions of the study even with the rhGH adverse events included for consideration are wrong.

Results from the study demonstrate benefit with the two drugs. Nandrolone (1.6-kg) and rhGH (2.5-kg) administration were associated with a significant increases in lean body mass (LBM) and fat free mass (FFM) than placebo by DEXA. However, body composition changes assessed by bioelectrical impedance (BIA) demonstrate a significant increase in LBM and a significant decrease in fat mass with rhGH administration but not nandrolone decanoate compared to placebo. Moreover, the changes with rhGH administration were significant when compared to nandrolone,

Whole body fat mass and subcutaneous fat volume significantly decreased with rhGH administration when compared to placebo. Additionally, the decrease in whole body fat mass and visceral fat volume with rhGH administration is significantly greater when compared to nandrolone. Nandrolone decanoate administration did not significantly change any of these parameters (whole body fat mass, visceral fat volume, and subcutaneous fat volume) compared to placebo.

In the words of the authors, "This randomized, placebo-controlled trial of nandrolone in HIV-infected men with mild to moderate weight loss represents the first, head-to-head comparison of an androgen with rhGH." Based upon the results of the study, the conclusion is, "Nandrolone and rhGH were both effective in increasing LBM in HIV-infected men with mild to moderate weight loss. rhGH is expensive and its administration is associated with high frequency of adverse events and treatment discontinuations due to adverse events. Therefore, an androgen regimen might be an attractive alternative or an adjunct to rhGH therapy because of its lower cost, lower frequency of adverse events, and greater potential for augmenting muscle strength and power." The study concludes, "[t]hat nandrolone is superior to placebo and not significantly different from a Food and Drug Administration-approved regimen of rhGH in improving lean body mass in HIV-infected men with mild to moderate weight loss."

The basis for nandrolone superiority, according to the authors, is rhGH cost, rhGH adverse events and treatment discontinuations, and greater potential for muscle strength. Regarding cost, the study did not discuss rhGH cost in comparison to nandrolone nor provide sources to support this contention. Nevertheless, even if one assumes for argument that rhGH cost is greater than nandrolone, this is relevant only if there is a proper benefit and harm analysis.

The authors state, "An AIDS Clinical Trials Group expert panel suggested that a 1.5-kg increase in LBM over baseline is clinically meaningful. Therefore, the 1.65-kg gain in nandrolone-treated men and 2.45-kg gain in LBM in rhGH-treated men might be viewed arguably as clinically significant." The 1.65-kg increase in LBM in the nandrolone group is marginally above the 1.5-kg floor recommended by the AIDS Clinical Trials Group expert panel. An important question is the sustainability of the LBM change by each drug, particularly nandrolone since the change is so marginal.

There is the very important and critical adverse event of HPTA suppression. In contrast to other studies, the investigators did not hide behind the cloak of cross reactivity as an inability to measure testosterone.[198] "Nandrolone administration was associated with greater reductions in LH, FSH, and total and free testosterone levels than placebo and rhGH." The reductions are significantly lower with each sex hormone. Importantly, total testosterone (nmol/liter) was 18.3 ± 1.0 (527 ng/dL) vs. 15.1 ± 1.3 (435 ng/dL) vs. 6.1 + 2.2 (176 ng/dL) for the control, rhGH, and nandrolone groups, respectively. By the study laboratory data alone, subjects receiving nandrolone decanoate have hypogonadotropic hypogonadism. This is inarguable. Induced hypogonadism by AAS administration and cessation has adverse effects that include a decrease in LBM and increased adiposity on body composition.

According to the study, 1.5-kg is the floor for any clinical meaningful increase in LBM. At the marginal 1.65-kg change with nandrolone, a decrease of more than 0.15-kg would place the nandrolone effect as clinically meaningless, by the measurement cited by the authors. The authors' discussion stated, "Serum LH and FSH levels were [significantly] suppressed by nandrolone administration; suppression of LH levels was associated with lowering of circulating total and free testosterone concentrations." "These data demonstrate that nandrolone is a potent androgen." These authors know that the effect of the ensuing hypogonadism results in a far greater loss than 0.15-kg LBM in the return to homeostasis.

This published report left no doubt as to the intent and purpose of investigators. In a study comparing the effects of nandrolone decanoate to recombinant human growth hormone (rhGH), the authors conclude that nandrolone is superior to placebo and not significantly different from a Food and Drug Administration approved regimen of rhGH in improving lean body mass in HIV-infected men with mild to moderate weight loss. This recommendation is tantamount to an imprimatur by major medical universities and widely recognized research investigators that a drug not approved by the FDA, nandrolone decanoate, is not only equivalent but also superior to an FDA approved drug, rhGH, for clinical use. This study has far-reaching implications to physician prescribing practices and patients prescribed nandrolone because of this study.

The conclusions of the study are incorrect, highlight questionable research practices, and place countless individuals' health and welfare in danger. This conclusion ignores data from their own study, crosses the boundary from questionable research practice to scientific misconduct, and poses an immediate threat to the health and welfare of any individual where put into clinical practice. This conclusion is shocking, horrific, and damaging.

In 1999, many of these same investigators published the results of administering nandrolone decanoate to eugonadal HIV+ men.[199] This nonplacebo-controlled, open label, randomized study was conducted to test the hypotheses that pharmacological doses of nandrolone decanoate would increase lean body tissue, muscle mass, and strength in HIV+ men, and that these effects would be enhanced with progressive resistance training (PRT).

Randomization of thirty human immunodeficiency virus-positive men was to groups both receiving weekly injections of nandrolone but with one group participating in progressive resistance training (PRT). The study design did not include a placebo control group. All subjects received nandrolone decanoate by weekly intramuscular injection for 16 weeks. The first dose of nandrolone was 200 mg, and the second dose was 400 mg. The dose was 600 mg for weeks 3–12. The investigators followed a dose reduction during weeks 13–16 (400, 200, 100, and 50 mg, respectively) to withdraw patients from pharmacological doses. They did not elaborate or discuss the purpose of the dose reduction in terms of withdrawal.

Total body weight increased significantly in both groups, with increases due primarily to augmentation of lean tissue. Lean body mass determined by dual energy x-ray absorptiometry increased significantly more in the PRT group. The authors conclude that pharmacological doses of nandrolone decanoate yielded significant gains in total weight, lean body mass, body cell mass, muscle size, and strength.

The data showed almost half (12/30) of the subjects experienced testicular shrinkage, implying Leydig cell dysfunction, decreased testosterone levels that would be expected from suppressed LH and FSH secretion. The authors admit this much, "The only common adverse effect was the self-reported testicular shrinkage that would be expected with high doses of androgens suppressing LH and FSH secretion."

The lack of sex hormone measurements is puzzling and troublesome in light of this clinical finding. In addition, the dose reduction schedule has no basis in the peer-reviewed

literature and is evidence that the authors are aware of problems after AAS cessation. Despite the clinical findings of testicular shrinkage and reducing the nandrolone dose, the study did nothing to monitor the adverse effects on sex hormone levels. As above, this is unsound research design and unsound research methodology. During the period of induced hypogonadism after AAS cessation, the anabolic improvements will be lost. What this study equates to is a test for an impaired host, HIV+ males, to withstand the comorbid condition of induced hypogonadism.

In the same year a similar study studying nandrolone decanoate administration did not fail to measure sex hormones. Strawford et al. investigated the, "Effects of nandrolone decanoate therapy in borderline hypogonadal men with HIV-associated weight loss."[200] The study consisted of a 21-day, double-blinded, randomized, placebo-controlled inpatient phase, followed by a 12-week open label treatment phase. Intramuscular injections were nandrolone decanoate (65 mg or 195 mg/week) or by placebo (sterilized sesame oil) for a period of 14 to 16 days. To achieve steady-state plasma levels of nandrolone rapidly, a loading dose (240 mg in the high-dose group, 80 mg in the low-dose group, and sesame oil in the placebo group) was administered IM on the first treatment day. Administration of injections of 19 mg or 56 mg nandrolone decanoate was every other day in the low and high-dose groups, respectively. Plasma nandrolone levels measurements were on the final 3 days of the study.

The study conclusions are that both low-dose and high-dose nandrolone resulted in significant nitrogen retention compared with placebo. Nandrolone decanoate therapy in the absence of an exercise program in HIV+ eugonadal men caused substantial nitrogen retention compared with placebo, similar in extent to the nitrogen retention previously achieved with recombinant growth hormone. The study further concludes, "It is reasonable to expand the criteria for androgen treatment . . . to include at least patients in the lowest quartile of serum [eugonadal] testosterone."

The nandrolone decanoate dose is markedly less than that in the study above that did not monitor or measure sex hormones. Average plasma nandrolone concentrations were 450±50 ng/ml (high dose) and 280±110 ng/ml (low dose). These nandrolone concentrations cause HPTA suppression. In low and high-dose nandrolone groups, the endogenous gonadal axis (testosterone, LH, and FSH) was suppressed, with no change in the placebo group ($P<.05$). Normal reference range is testosterone 225-900 ng/dL, LH 0.4-5.7, and FSH 1.1-13.5.

Change in gonadal hormone status during treatment phase

**$P<0.05$		Placebo	Low dose ND	High does ND
Testosterone (ng/dL)				
	Posttreatment	461 (104)	**68 (10)	**113 (5)
	Δ	66 (55)	-276 (124)	-284 (35)
LH (mIU/ml)				
	Posttreatment	2.8 (0.9)	0.3 (0.1)	**0.0 (0.0)

	Δ	-0.4 (0.7)	-2.7 (0.8)	-3.3 (1.0)
FSH (mIU/ml)				
	Posttreatment	3.2 (0.9)	1.0 (0.4)	**1.1 (0.4)
	Δ	-1.4 (0.6)	-4.6 (1.7)	-4.7 (1.3)

Most studies of the efficacy of the oral androgen oxandrolone have been small, observational, or unpublished.[201] In 1999, Strawford et al. conducted a study to determine whether a moderately supraphysiologic androgen regimen, including an anabolic steroid, would improve LBM and strength gains of progressive resistance exercise (PRE) in HIV-infected men with prior weight loss (mean, 9% body weight loss) and whether protease inhibitor antiretroviral therapy prevents lean tissue anabolism.[202] Study support included Biotechnology General Corporation, manufacturer of oxandrolone.[203]

For 8 weeks, all subjects received supervised PRE with physiologic intramuscular testosterone replacement (100 mg/wk) to suppress endogenous testosterone production. Randomization was between an anabolic steroid, oxandrolone, 20-mg/day, and placebo. Outcome measurements include lean body mass, nitrogen balance, body weight, muscle strength, and androgen status.

Both groups showed significant nitrogen retention and increases in LBM, weight, and strength. The mean (SD) gains were significantly greater in the oxandrolone group than in the placebo group of nitrogen per day, LBM, and strength gains for various upper and lower body muscle groups by maximum weight lifted and dynamometry. The study, in eugonadal men, concludes, "A moderately supraphysiologic androgen regimen that included an anabolic steroid, oxandrolone, substantially increased the lean tissue accrual and strength gains from PRE, compared with physiologic testosterone replacement alone, in eugonadal men with HIV-associated weight loss."

In this small study, important considerations presented in the results directly affect the primary outcome measures. First, the use of AAS produces adverse effects that include liver enzyme abnormalities. Two subjects in the oxandrolone group had elevations in liver function test results. Second, because of these adverse effects, prescribing AAS is self-limited and discontinuation must occur. One subject in the oxandrolone group discontinued the study because of elevated liver function test results. Third, upon AAS cessation a period of hypogonadism ensues, anabolic steroid induced hypogonadism (ASIH).

This study is particularly elegant for the measures taken that demonstrate conclusively HPTA suppression, even in the presence of testosterone administration. Administration of testosterone is to both groups in order to equalize any effects of testosterone between groups. Serum total testosterone levels were within the normal range and were not significantly different between groups or from baseline.

The endogenous gonadal axis was suppressed in both groups compared with baseline, with significant decreases in luteinizing hormone ($P<0.001$) and follicle-stimulating hormone levels ($P<.001$), but there were no differences between groups. The urine testosterone to

epitestosterone ratio is an index of exogenous testosterone administration. The testosterone to epitestosterone ratio was similar to published normal values in both groups at baseline and increased significantly from baseline in both groups. The significantly greater increase in testosterone to epitestosterone ratio in the oxandrolone group compared with the placebo group suggests that residual endogenous androgen synthesis in the presence of testosterone replacement alone was more completely suppressed by the addition of oxandrolone. Thus, HPTA suppression occurred with both groups but more significantly with the addition of oxandrolone.

In 2006, Bhasin published with other colleagues published a study of oxandrolone in the treatment of HIV-associated weight loss in men.[204] Grant support provided solely by Biotechnology General (now Savient Pharmaceuticals). Biotechnology General provided the statistical analysis using the study's predetermined criteria and performed secondary analyses.

The study was to evaluate the efficacy and safety of oxandrolone in promoting body weight gain in HIV-associated weight loss. In a randomized, double blind, placebo-controlled trial, two hundred sixty-two HIV+ men were randomized to placebo or to 20, 40, or 80 mg of oxandrolone daily for 12 weeks. The study, conducted between the autumn of 1996 and the summer of 1998, was “the largest randomized placebo-controlled trial of an androgen in patients with HIV-associated weight loss.”

Two hundred sixty-two patients were randomized and included in the intent-to-treat analysis (placebo [n = 65], 20mg of oxandrolone [n = 64], 40 mg of oxandrolone [n = 65], and 80 mg of oxandrolone [n = 68]). Of these, 195 subjects completed the double-blind phase and 193 completed the open-label phase. Of the 67 subjects who discontinued treatment during the double-blind phase, 12 were in the placebo group and 55 in the oxandrolone groups (18 in the 20-mg, 18 in the 40-mg, and 19 in the 80-mg). Reasons for discontinuations included adverse experience, death, intercurrent medical problem or disease-related complication, subject relocation or voluntary patient withdrawal, and noncompliance.

The study reinforces that AAS treatment is of limited duration. Certain adverse effects demand and require AAS discontinuation. Among these are liver function abnormalities and lipid profile changes. The investigators noted that levels of AST and ALT liver enzymes increased. Grade III and IV elevations of transaminases were observed in >5% of study participants.[205] Furthermore, there was a significant increase in low-density lipoprotein (LDL) cholesterol levels at the 40-mg and 80-mg doses and a significant decrease in high-density lipoprotein (HDL) cholesterol levels at all doses.

The findings include, “Oxandrolone treatment was associated with significantly greater body weight gain above baseline than with placebo. A major portion of this weight gain occurred in the lean body compartment.” The publication conclusion states, "Oxandrolone administration is effective in promoting dose-dependent gains in body weight and BCM in HIV-infected men with weight loss."

In this study, also, serum testosterone and LH concentrations significantly decreased from baseline at all doses of oxandrolone but not with placebo treatment. Oxandrolone treatment was associated with significant suppression of luteinizing hormone and testosterone levels, both

total and free. The singular conclusion, inarguable, is the presence of HPTA suppression leading to a period of hypogonadism after AAS cessation.

In 2005,[206] a telling study demonstrates the use of anabolic steroids, oxandrolone, is only equal to progressive resistance training (PRT) as treatment for AIDS wasting. Oxandrolone and PRT induce similar improvements in body composition, but PRT improves quality of life more than nutrition or oxandrolone, particularly among patients with impaired physical functioning (PF). PRT was the most cost-effective intervention, and oxandrolone was the least cost-effective intervention.

The study compared oxandrolone or strength training with nutrition alone (NA) for AIDS wasting. Randomization of patients were to (1) nutrition alone with placebo pills, (2) nutrition with 10 mg of oxandrolone administered orally twice a day, or (3) nutrition with progressive resistance training (PRT) for 12 weeks.

The oxandrolone and PRT subjects had increases in midthigh cross-sectional muscle area (CSMA), although these increases did not differ significantly from the NA arm. Only PRT caused significant improvements in PF and seven measures of strength (P values: 0.04 to <0.001). There were no overall differences between groups in PF change. Among patients with impaired baseline PF, however, oxandrolone was significantly less effective than NA and PRT was significantly better than NA. All treatments led to increases in protein intake and performance; NA and PRT increased caloric intake.

The above study does not take into consideration ASIH, published literature in 2004 that shows the loss of anabolic improvements after oxandrolone cessation,[207] and other hypogonadal effects. Including these effects, clearly the indications for AAS treatment disappear.

Prominent among publications studying the AAS oxymetholone in HIV+ males are those of Hengge et al. In 1996, Hengge et al. published the findings oxymetholone promotes weight gain in patients with advanced human immunodeficiency virus (HIV-1) infection.[208] Hengge tested oxymetholone in a thirty week unblinded, randomized study alone or in combination with ketitofen, a tumor necrosis factor (TNF) inhibitor. TNF is thought to possibly contribute to the weight loss seen with AIDS. Oxymetholone was safe and promoted weight gain in cachectic patients with advanced HIV-1 infection. The addition of ketotifen did not support further weight gain. There are no sex hormone measurements in the study.

A number of publications do contain results for the sex hormones during oxymetholone administration. These studies establish the HPTA suppressive effects of oxymetholone administration. In 2003, Hengge et al. results from two published studies are from the same population.[209] The study is a randomized, placebo controlled phase III study of oxymetholone. Patients were randomized to receive the anabolic steroid oxymetholone [50 mg twice (BID) or three times daily (TID)] or placebo for 16 weeks followed by open-label treatment.

Oxymetholone led to a significant weight gain in the TID and BID groups ($P<0.05$ for each treatment versus placebo). Patients in the placebo group gained 1.0-kg compared to 3.0-kg among those receiving therapy three times daily and 3.5-kg among those receiving therapy twice

daily. The most important adverse event was liver-associated toxicity. Overall, 35% of patients in the TID, 27% of patients in the BID oxymetholone group and no patients in the placebo group had a greater than five times baseline increase for alanine aminotransferase during the double-blind phase of the study. Two patients in the oxymetholone TID arm discontinued due to elevated liver enzymes.

Determinations of serum total testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) every 4 weeks during the 16-week studies were found to decrease markedly and significantly upon the intake of oxymetholone. All patients in the trial were eugonadal at the beginning of the trial. Total serum testosterone significantly declined in patients receiving oxymetholone BID or TID by 71% and 59%, respectively (each $P<.0001$). There was a parallel significant decline of LH and FSH, the regulators of testosterone production and gonadal function.

LH and FSH are the regulators of testosterone production and spermatogenesis, respectively. AAS administration causes a decrease in the serum gonadotropin, LH, level that in turn is reflected in a decrease in serum testosterone. The result of an abnormally low total testosterone in the face of an abnormally low LH is diagnostic for hypogonadotropic hypogonadism. The etiology is clear, anabolic steroid induced hypogonadism.

There is not a single published study demonstrating an absence of HPTA suppression with AAS administration that does not continues after AAS cessation. The studies discussed thus far demonstrate HPTA suppression for nandrolone, oxandrolone, and oxymetholone. By all available published literature, AAS administration induces a state of hypogonadism after their cessation, including testosterone.

Bhasin and colleagues have published a number of studies of testosterone supplementation to effect positive body composition changes in HIV+ males. None of the studies consider the period after AAS cessation. Not surprisingly, the studies consistently and uniformly conclude that testosterone administration increases LBM and muscle strength, decrease adiposity, and are safe and effective forms of treatment for HIV+ weight loss.

In 2000, Bhasin et al. published the effects of testosterone replacement with and without resistance exercise on muscle strength and body composition in HIV+ men with low testosterone levels and weight loss.[210] The study is a randomized double blind placebo-controlled clinical trial of 61 HIV+ men, 49 of who completed the study, with serum testosterone levels of less than 12.1 nmol/L (349-ng/dL) and weight loss of 5% or more in the previous 6 months. Randomization of participants was to four treatment groups: (1) placebo with no exercise; (2) placebo with exercise; (3) testosterone enanthate with no exercise; or (4) testosterone enanthate with exercise. Treatment duration was 16 weeks. Testosterone enanthate administration was 100 mg/week, intramuscularly.

Body weight increased significantly by 2.6 kg ($P<.001$) in men receiving testosterone alone and by 2.2 kg ($P=.02$) in men who exercised alone but did not change in men receiving placebo alone (-0.5 kg; $P=.55$) or testosterone and exercise (0.7 kg; $P=.08$). Average lean body mass (LBM) significantly increased in testosterone enanthate with no exercise and testosterone

enanthate with exercise. Average LBM in exercise alone almost increased to significant levels. The placebo with exercise, testosterone enanthate with no exercise, and testosterone enanthate with exercise treatment groups experienced significant increases in maximum voluntary muscle strength in leg press, leg curls, bench press, and latissimus pulls.

The authors, "[s]uggest that testosterone and resistance exercise promote gains in body weight, muscle mass, muscle strength, and lean body mass in HIV-infected men with weight loss and low testosterone levels." Also included is the statement, "Testosterone and exercise together did not produce greater gains than either intervention alone." In other words, exercise alone is sufficient to produce the positive body composition changes seen with the addition of testosterone.

At the conclusion of the clinical trial, any change in homeostasis necessarily infers disease. At week 16, both total and free testosterone levels increased significantly from baseline in the testosterone treatment groups. Serum luteinizing hormone (LH) levels decreased significantly in the testosterone treatment groups from baseline. These changes must return to baseline levels before homeostasis returns. During this period, induced hypogonadism, adverse body composition changes will directly affect the study results and the conclusions drawn.

Changes in Sex Hormone Levels

	No Exercise		Exercise	
	Placebo	Testosterone	Placebo	Testosterone
Testosterone, nmol/L***				
Baseline	6.1 (0.7)	7.1 (0.8)	7.0 (1.0)	7.0 (1.2)
Week 16	5.0 (0.5)	11.7 (1.6)	7.4 (1.2)	10.8 (1.9)
Δ	-1.2 (0.6)	*4.5 (1.8)	0.4 (1.0)	*3.8 (2.1)
P value	.70	.02	.57	.02
LH, IU/L				
Baseline	5.0 (1.0)	3.4 (0.4)	4.3 (0.9)	6.6 (2.0)
Week 16	3.7 (0.8)	0.3 (0.1)	4.6 (1.0)	0.6 (0.3)
Δ	-1.4 (0.7)	**-3.1 (0.4)	0.3 (0.2)	**-6.0 (1.8)
P value	.17	<.001	.39	<.001
FSH, IU/L				
Baseline	5.8 (1.8)	4.5 (0.5)	7.1 (1.9)	8.6 (2.6)
Week 16	5.0 (2.0)	0.5 (0.2)	6.7 (1.6)	2.0 (1.2)
Δ	-0.8 (0.8)	-4.2 (0.4)	-0.4 (0.7)	-6.5 (1.6)
P value	.20	.05	.46	.05

Significance levels: *P<0.05 vs. placebo, no exercise; **P<0.05 vs. placebo, no exercise, and placebo with exercise; ***Overall ANOVA P<0.03

In 1998, they examined, "Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels."[211] Study support provided primarily by a research grant from SmithKline Beecham Pharmaceuticals Co.[212] Androderm is a testosterone patch marketed by SmithKline Beecham Pharmaceuticals.

This is a collaborative effort from well-known institutions, including Charles R. Drew University of Medicine and Science, Los Angeles, California; Harbor-University of California-Los Angeles Medical Center; University of California School of Medicine, Los Angeles, California; and Karolinska Institute, Stockholm, Sweden.[213]

Randomly assigned HIV+ men with serum testosterone levels below 400-ng/dL received (1) two placebo patches or (2) two testosterone patches designed to release 5 mg testosterone over 24 hours for 12 weeks. Parameters monitored include lean body mass, body weight, muscle strength, health-related quality of life, and HIV-disease markers.

Total body weight did not change in either treatment group. Lean body mass did not change in the placebo group, but increased significantly in the testosterone-treated men. However, there was no significant difference between the two treatment groups in the change in lean body mass. Fat free mass (FFM) increased significantly in the testosterone group, but not in the placebo group. The change in FFM was not significantly different between the two treatment groups. Fat mass, estimated as the difference between total body weight and FFM, decreased in the testosterone-treated men, but increased in the placebo-treated men.

In the study, a conclusion made is, "Testosterone replacement in HIV-infected men with low testosterone levels is safe and is associated with a gain in lean body mass . . . ." Serum testosterone levels significantly increased in the testosterone-treated, but not in the placebo-treated, men. The safety asserted does not include consideration that serum LH levels significantly decreased in the testosterone-treated, but not in the placebo-treated, men.

Mean serum testosterone, LH, and FSH levels during the screening and treatment periods and change from baseline levels

Group	Pretreatment	Week 12	Change from baseline
Testosterone (ng/dL)			
Placebo	211± 18 (21)	218± 24 (18)	10 ± 16 (18)
Testosterone	258± 11 (20)	364± 42 (14)	*100 ± 39* (14)
LH (IU/L)			
Placebo	7.3± 2.6 (21)	3.8± 0.6 (18)	-0.9± 0.5 (18)
Testosterone	6.6± 0.7 (20)	2.9± 0.5 (14)	**-4.0 ± 0.7 (14)
FSH (IU/L)			
Placebo	9.6± 2.4 (21)	4.7± 0.6 (18)	-2.1± 0.4 (18)
Testosterone	7.8± 0.9 (20)	3.6± 0.5 (14)	***-4.0 ± 0.7 (14)

Significance levels: *P=0.0449, comparison of change in total testosterone levels from baseline between the two group. **P=0.001, change from baseline in testosterone group vs. change in placebo group. ***P=0.0146, change from baseline in testosterone group vs. change in placebo group.

Data are the mean ± SE. Pretreatment value = average of screen 1 value and day 1 value. Change from baseline = week 12 value minus the mean pretreatment value. For total testosterone, mean pretreatment = averaged pretreatment testosterone value (average of screen 1 value, screen 2 value, and day 1 value). Change from baseline = week 12 value minus the mean pretreatment value. The normal range for LH is 2–11 IU/L, FSH is 1–9 IU/L, and total testosterone is 300–1000 ng/dL.

The investigators are from renowned research institutions, most with board certification in internal medicine, many board certified in the subspecialty endocrinology, and most critical, publishing data regarding HPTA physiology. These very same investigators now wish to feign they are ignorant of hypogonadism after AAS cessation, ignorant of the effects of hypogonadism on body composition, and ignorant that this would have an effect upon the published data and any conclusions drawn. Rather than improve the health of HIV+ males, the AAS treatments after their cessation place them in a state of health than when first administered AAS.

- 6 -

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) is primarily a disease of the elderly thus placing those affected at a higher risk of morbidity and mortality. Any additional comorbid disease will undoubtedly lead to additional adverse outcomes, not less. In already compromised individuals, hypogonadism, whether or not induced, is a disease with associated particularly significant adverse events that is clearly such a comorbid condition. There can be no plausible reason or justification, none, to expose COPD individuals to AAS treatment without consideration for the period of hypogonadism after AAS cessation. Yet, a number of published studies utilizing AAS treatment completely ignore this period that not only endangers the subjects but also additionally affects adversely the results and conclusions of the studies. The basis for AAS treatment of COPD individuals is tenuous at best and at worst an enterprise of conflicted physicians looking for academic and financial rewards.

Chronic obstructive pulmonary disease (COPD) refers to two lung diseases, those being chronic bronchitis and emphysema. Characterization of both diseases is obstruction to airflow that interferes with normal breathing. Both of these conditions frequently co-exist, hence physicians prefer the term COPD. COPD is the fourth leading cause of death in America. In 2004, estimates are that 11.4 million U.S. adults (aged 18 and over) have COPD.[214]

Chronic bronchitis is the inflammation and eventual scarring of the lining of the bronchial tubes. When the bronchi are inflamed and/or infected, less air is able to flow to and from the lungs and coughing may produce a heavy mucus or phlegm. The condition is defined by the presence of a mucus-producing cough most days of the month, three months of a year for two successive years without other underlying disease to explain the cough.

Emphysema begins with the destruction of air sacs (alveoli) in the lungs where there is from the air exchange of oxygen for carbon dioxide in the blood. The walls of the air sacs are thin and fragile. Damage to the air sacs is irreversible and results in permanent "holes" in the tissues of the lower lungs. With continued destruction of air sacs, the lungs are able to transfer less and less oxygen to the bloodstream, causing shortness of breath. The lungs also lose their elasticity, which is important to keep airways open. This translates into the patient experiencing great difficulty exhaling.[215]

The **G**lobal Initiative for Chronic **O**bstructive **L**ung **D**isease (**GOLD**) is a collaborative project of the U.S. National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO).[216] Its goals are to increase awareness of COPD and decrease morbidity and mortality from this disease. GOLD aims to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage a renewed research interest in this extremely prevalent disease.

The GOLD Workshop Report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, presents a COPD management plan with four components: (*1*) Assess and Monitor Disease; (*2*) Reduce Risk Factors; (*3*) Manage Stable COPD; (*4*) Manage Exacerbations. The Workshop Report is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. Individuals with expertise in COPD research and patient care developed the report. Before its release for publication, the NHLBI and the WHO reviewed the Workshop Report.

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, dyspnea (abnormal shortness of breath), and/or a history of exposure to risk factors for the disease. Chronic cough and sputum production often precede the development of airflow limitation by many years, however, not all individuals with cough and sputum production go on to develop COPD.

Confirmation of the diagnosis is by spirometry. Spirometry is the use of techniques or an instrument for determining the capacity of the lungs. Spirometry can provide a preliminary and objective evaluation of lung volumes for comparison to normal or predicted values. Forced vital capacity (FVC) and the forced expiratory volume at 1 second (FEV1.0) are useful parameters in COPD diagnosis. FVC is the total volume of air exhaled after a maximal inhalation employing maximal speed and effort. The FVC is a valuable screening device for pulmonary impairments. The volume of air expired in the first second is termed the forced expiratory volume at 1 second, which is abbreviated as FEV1.0. The presence of a postbronchodilator FEV_1 <80% of the predicted value in combination with an (FEV_1/FVC) <70% confirms the presence of airflow limitation that is not fully reversible.

COPD is a multisystem disease. The systemic consequences of COPD result in a number of factors that include decreases in BMI and exercise tolerance. The decline in BMI in patients with COPD is a marker of advanced disease, corresponding to a currently unknown factor or factors that are also responsible for the decline in pulmonary function and progression of the disease. Hypoxia (decreased oxygen) and hypercapnia (increased carbon dioxide) are related to the severity of COPD and have been linked to malnutrition.[217] Similar associations have been found for low diffusion capacity and increased total lung capacity (TLC), suggesting pathogenic factors for emphysema similar to those for weight loss.[218]

Survival studies in selected groups of patients with chronic obstructive pulmonary obstruction (COPD) and in population-based studies have consistently shown higher COPD-related mortality rates in underweight and normal-weight patients than in overweight and even

obese patients.[219] Fat-free mass is an independent predictor of mortality irrespective of fat mass and acts as a systemic marker of disease severity in COPD staging.[220]

Rehabilitative programs of exercise training increase exercise tolerance substantially.[221] Endurance training increases endurance (e.g., walking, climbing stairs), whereas progressive resistance training increases strength (e.g., standing from a sitting position, maintaining balance), although modest crossover effects can be seen in some measures of strength and endurance.[222] Endurance training increases muscle capillarity and aerobic enzyme concentrations without much hypertrophy, and resistance training increases muscle fiber cross-sectional area without much increase in capillarity or aerobic enzyme concentration.

Patients with chronic obstructive pulmonary disease (COPD) often have exercise intolerance as their chief complaint.[223] In recent years, it has become clear that dysfunction of the muscles of ambulation contributes to exercise intolerance in these patients.[224] This is of great importance, as muscle dysfunction is potentially remediable. Androgenic steroids induce changes in the muscles of ambulation at least superficially similar to those seen with resistance training.[225] Testosterone supplementation increases muscle mass and improves maximal voluntary muscle strength.[226]

Since exercise-training interventions are a cornerstone in pulmonary rehabilitation and yield benefits, at least in part, by improving the function of the exercising muscles, it seems reasonable to hypothesize those pharmaceutical agents that improve muscle function in similar ways might be useful adjuncts to rehabilitative therapy.[227] Thus, the logic of the authors is AAS treatment will be of benefit.

It is potentially a dangerous and ill-conceived notion to draw the consequences of a disease as the reasons for causation. It is a stretch to propose AAS treatment simply because a disease manifestation is a decrease in exercise tolerance, loss of muscle mass, or decreased muscle strength. It is true that there is a clear direct relation between testosterone and muscle, but other than true hypogonadism and only under the strictest and clearly defined parameters can AAS administration be justified. Symptomatic relief is a consideration in treatment but it is absurd, arrogant, and abusive to propose that AAS treatment in eugonadal subjects will somehow change the pathophysiology of a disease barring credible scientific evidence. Yet, this is precisely the basis for the studies published below.

In 2002, Yeh et al. published the study, "Reversal of COPD-associated weight loss using the anabolic agent oxandrolone."[228] The study is from the Veterans' Affairs Medical Center (Dr. Yeh), Northport, NY; and Bio-Technology General Corporation (Ms. DeGuzman and Dr. Kramer), Iselin, NJ. Study support provided by Bio-Technology General Corporation. Significantly, Dr. Kramer and Ms. DeGuzman are employees of Bio-Technology General.

Oxandrolone is an oral anabolic steroid approved as an adjunct to help restore weight to patients who have lost weight due to chronic infection, severe trauma, extensive surgery, or who fail to gain or maintain weight due to unknown pathophysiologic reasons, and to help offset the catabolism associated with the long-term use of corticosteroids.[229] While the ratio of anabolic to

androgenic potency with testosterone is 1:1, the ratio of these effects with oxandrolone is between 3:1 and 13:1.[230]

A total number of 128 patients enrolled in the study. Disposition of patients was the following: 49 completed 4-month participation, 28 requested removal from study, 7 unavailable for follow-up, 4 noncompliance, 34 adverse event, 4 death, and 2 other (not specified). Although 49 patients completed the entire 4 months of oxandrolone therapy, data for another 6 patients who discontinued between month 2 and month 4 were captured and carried forward. Analyses of the data of 55 patients are included in this report. Thus, 73 discontinued the study.

Adverse events considered by the investigator to be possibly or probably related to oxandrolone. Forty-nine patients (38%) had one or more events. Of those that discontinued the study included 11.5% from elevated transaminases. The intracerebral hemorrhage occurred due to over anticoagulation in a patient receiving warfarin, a known drug interaction of anabolic steroids. This resulted in the only oxandrolone-related death. The total number of patients discontinued due to adverse experiences was 34, 22 of which were associated with oxandrolone.

Yeh and colleagues administered 4 months of oral oxandrolone to underweight COPD men and women. Weight gain averaged 2.1 kg. Neither maximum inspiratory pressure nor 6-minute walk distance increased significantly. The study did not include measurements of sex hormones despite the widespread and common knowledge that AAS adversely affect the HPTA. This study, while not including sex hormone measurements, does demonstrate the adverse effects of AAS treatment necessitate AAS discontinuation. After AAS discontinuation, a period of hypogonadism will ensue with negative consequences upon the body composition results of the study. These will, without a doubt, result in the significant findings of AAS administration to disappear with the added medical concerns of hypogonadism now facing the patient.

Since 1997, other publications of a number of randomized controlled trials (RCT) have appeared in which there is administration of testosterone or its analogs (anabolic steroids) to patients with COPD. In each of these studies, there are no significant differences from placebo for AAS administration in functional measures for COPD.

Creutzberg and colleagues administered **nandrolone decanoate** or placebo by IM injection every 2 weeks for 8 weeks to 63 men with COPD.[231] Fat-free mass increased by 1.7 kg in the nandrolone group compared to 0.3 kg in the placebo group. No significant differences were seen between groups in incremental cycle ergometer exercise capacity or health related quality of life (HRQOL). Muscle strength was assessed, but no differences were detected in handgrip strength or isokinetic leg strength testing results.

Svartberg and colleagues administered **testosterone enanthate** or placebo by injection every 4 weeks for 26 weeks to 29 men with COPD.[232] DEXA scanning revealed a 1.1-kg increase in lean mass and a 1.5-kg decrease in fat mass in the testosterone group. No exercise outcomes were assessed. No difference in quality of life, as assessed by the St. George respiratory questionnaire was detected, but better sexual quality of life and erectile function was noted.

Schols and colleagues administered nutritional supplementation with and without nandrolone decanoate for 8 weeks to approximately 130, male and female, patients with COPD.[233] Weight gain was approximately 1.5 kg in both groups, but weight gain was mostly fat mass in the nutrition-alone group and mostly lean mass in the nandrolone + nutrition group. No differences were detected in maximum inspiratory pressure and 12-minute walking distance between treatment groups.

In 2004, Casaburi et al. published a study, "Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease."[234] Of interest is the journal publications include a conflict of interest statement. For this study, conflict of interest included Richard Casaburi, lead author is on the Biotechnology General Corporation (BTG) National Advisory Board (honorarium $750 to date) and has also been site principal investigator in a multicentered trial of Oxandrolone (an oral steroid) in COPD sponsored by BTG (total payments to site of approximately $75,000), and BTG has donated testosterone enanthate for this project (value approximately $700) and also markets Oxandrolone. Shalender Bhasin has received research grant support from Solvay Pharmaceuticals ($600,000) and ALZA Corporation ($150,000) and has served on Solvay's Advisory Board and served as a consultant ($5,500) and has given lectures that have been sponsored by BTG, Solvay, Watson, and ALZA Corporation ($10,000), and these corporations manufacture testosterone analogues or delivery systems for testosterone or its analogues.

The study aim is to determine whether testosterone supplementation might have the potential to be an appropriate adjunctive treatment during a program of pulmonary rehabilitation specifically directed at improving muscle mass and muscle function. The study is a randomized, placebo-controlled, 10-week trial of replacement doses of testosterone enanthate. The study is a comparison of the effects of this intervention with those of a standardized rigorous program of resistance training of the lower extremities and determined whether testosterone amplified the benefits of resistance training. Principal outcome measures included a change from baseline in body composition and muscle strength. Results also include the hormonal responses, changes in the levels of circulating indices of inflammation, and a number of safety measures.

The study examined the effects of testosterone supplementation (testosterone enanthate 100 mg/week for 10 weeks) with or without resistance training (45 minutes three times weekly) on body composition and muscle function. Screening serum testosterone was 400-ng/dl or less. Randomization of subjects were to four groups: (1) placebo injections + no training, (2) testosterone injections + no training, (3) placebo injections + resistance training, or (4) testosterone injections + resistance training. The baseline serum testosterone (mean ± SD) for the groups is 302 ± 154 (placebo injections + no training), 302 ± 89 (testosterone injections + no training), 277 ± 106 (placebo injections + resistance training), and 408 ± 139 (testosterone injections + resistance training).

The study findings include the lean body mass (LBM) significantly increased in testosterone treatment groups. The table included detailing the body composition results also includes the legend statements: *Response to intervention significantly different from nontestosterone groups and **Response to intervention significantly different from placebo + strength training group.

Body composition (in kg) responses to the interventions (Mean ± SD)

	Placebo + No Training		Testosterone + No Training		Placebo + Resistance Training		Testosterone + Resistance Training	
	Before	After	Before	After	Before	After	Before	After
Total fat	23.14 ± 7.86	23.06 ± 7.71	23.76 ± 8.97	***22.75 ± 8.69**	23.56 ± 11.43	23.43 ± 12.18	27.36 ± 15.48	***25.95 ± 16.14**
Total lean	49.01 ± 6.88	48.80 ± 6.27	52.04 ± 8.26	***54.34 ± 8.47**	50.94 ± 8.24	51.14 ± 8.53	52.33 ± 9.48	***55.62 ± 10.10**
% Fat	30.60 ± 7.41	30.58 ± 6.94	29.53 ± 6.68	****27.76 ± 6.07**	29.48 ± 6.95	28.83 ± 7.78	31.35 ± 10.08	***28.39 ± 10.36**

The study findings include the increase in one-repetition maximum leg press strength significantly increased in testosterone treatment groups and resistance training alone. Table legend statements: *Response to intervention significantly different from placebo + no training group and **Response to intervention significantly different from nontraining groups.

Leg press (kg) One-repetition maximum (1-RM) before and after the interventions (Mean ± SD)

Placebo + No Training		Testosterone + No Training		Placebo + Resistance Training		Testosterone + Resistance Training	
Before	After	Before	After	Before	After	Before	After
268 ± 62	274 ± 66	264 ± 89	***296 ± 73**	296 ± 96	***344 ± 98**	270 ± 141	****329 ± 167**

The data analysis methodology for the study is pretreatment values and the difference between pretreatment and post-treatment responses is by analysis of variance.[235] However, upon examination of the tables (pertinent results duplicated) showing results for each group it is not possible to calculate significant differences between or among groups using either the student t-test or a one-way analysis of variance (ANOVA). In fact, significance levels do not come close to the minimum significance level of 0.05 (a one in twenty chance that the results would occur randomly). It is relevant that there appear no actual significance *P*-levels within the study.

The study authors conclude, "The results show that replacement doses of testosterone increase lean body mass and strength in men with severe COPD and low testosterone levels" and "This is the first demonstration that strength increases accompany androgenic steroid supplementation in COPD and raises the possibility that testosterone supplementation may be appropriate therapy in conjunction with rehabilitative programs for patients with muscle weakness."

A brief discussion of the muscle mass and muscle strength changes above demonstrate that the study claims of significance differences between the no treatment groups and

testosterone treatment groups is questionable, if not false. Nonetheless, these differences do not translate into meaningful therapeutic changes. There was no demonstration of improvements in incremental or constant-work-rate cycle ergometer exercise.

Additionally, the authors state repeatedly that the proffered changes occur in men with "low testosterone levels." Further, the investigators state, "In this initial investigation of testosterone administration to men with COPD, we focused on men whose testosterone level was somewhat low (though normal ranges are difficult to define)." The authors' own clarification within parentheticals exposes the use of doublethink and obfuscation.

Even a cursory review of the study reveals the nature of this statement to be anything but true. The study states, "Patients were entered into the study based on testosterone level at initial screening (≤400-ng/dl)." Of the 85 men screened for the study, 40% had serum testosterone levels below the lower limit of the normal range for healthy young men (300-ng/dl); an additional 16% had low normal testosterone levels (300–400 ng/dl). The authors admit in a response to their study that 44% had testosterone levels >400-ng/dl and 86% had testosterone levels below the mean level for healthy young men (585-ng/dl). [236]

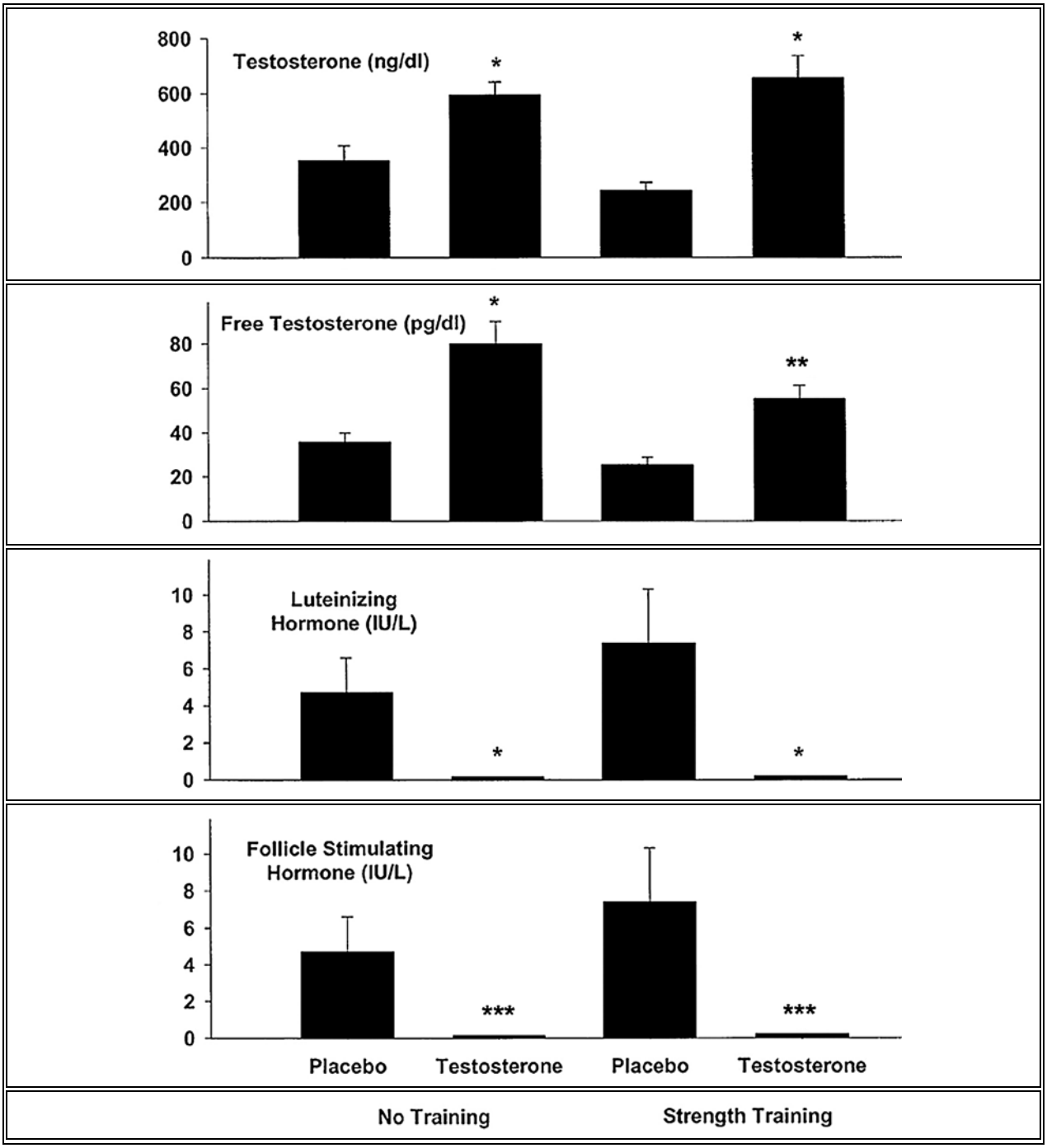
The study found that interventions were well tolerated with no abnormalities in safety measures. However, it is obvious that a safety measure not included is the basic physiological mechanism homeostasis. HPTA suppression is present, shown by the markedly and significantly reduced luteinizing hormone level.

In the two groups receiving placebo injections, there were no significant changes in total testosterone or in luteinizing hormone from preintervention values. Testosterone levels significantly increased in the groups receiving testosterone but not placebo. In the two groups receiving testosterone, there is significantly suppression of luteinizing hormone to very low levels. Testosterone supplementation resulted in near complete suppression of circulating levels of luteinizing hormone. This reflects the inhibitory effects of the elevated testosterone levels on pituitary secretion and secondarily endogenous testosterone secretion by the testes.

The study includes a figure (shown below) that displays hormonal levels from venous blood samples drawn immediately before weekly injections (nadir levels) for the four study groups. The figure legend statements: *****Response to intervention significantly different from nontestosterone groups; ******Response to intervention significantly different from testosterone + no training group; and *******Response to intervention significantly different from placebo + resistance training group.

In the two groups receiving placebo injections, there were no significant changes in total testosterone or in luteinizing hormone from preintervention values. Testosterone levels significantly increased in the groups receiving testosterone but not placebo. In the two groups receiving testosterone, there is significant and near complete suppression of circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Hormonal levels from venous blood samples drawn immediately before weekly injections (nadir levels) for the four study groups.



The authors admit, "This reflects the inhibitory effects of the elevated testosterone levels on pituitary secretion and secondarily endogenous testosterone secretion by the testes." HPTA suppression is present, shown by the markedly and significantly reduced luteinizing hormone level. As discussed previously, these hormone levels are significant for demonstrating anabolic steroid induced hypogonadism. Upon AAS cessation, ASIH will ensue.

Ferreira and colleagues studied the influence of oral anabolic steroids with COPD on body mass index (BMI), lean body mass (LBM), anthropometric measures, respiratory muscle strength, and functional exercise capacity among subjects with COPD.[237] The study is a prospective, randomized, controlled, double-blind study. The study group received 250 mg of testosterone i.m. at baseline and 12 mg of oral stanozolol a day for 27 weeks, during which time the control group received placebo.

AAS administration was associated with increases in BMI, LBM, and anthropometric measures of arm and thigh circumference, with no significant changes in endurance exercise capacity (maximum inspiratory pressure, 6-minute walk distance, or peak oxygen uptake).

LH and Testosterone Levels in Control and Study Groups

Mean (SEM)	Baseline	Week 9	Week 18	Week 27
LH, IU/L				
Control	5.7 (1.7)	7.2 (2.3)	7.1 (1.8)	7.4 (2.0)
Intervention	3.3 (0.6)	*§0.66 (0.2)	§1.8 (0.7)	§2.1 (0.8)
Testosterone, ng/dL				
Control	496 (117)	452 (43)	463 (31)	402 (89)
Intervention	415 (34)	*§157 (28)	*§135 (14)	*220 (31)

Levels of LH and testosterone were similar in both groups at baseline. The between-group differences for LH showed significant decreases in those receiving anabolic steroids at week 9, 18, and 27. During the administration of stanozolol, testosterone levels decreased significantly at weeks 9, 18, and 27 from baseline. Testosterone levels were significantly lower in the study group compared with the control group at 9 and 18 weeks. At week 27, the differences between groups were not statistically significant even though the levels of testosterone in the anabolic steroid group were comparable to prepubertal levels. Upon AAS cessation, ASIH will ensue. The table below includes the study results. Table legend statements: *$P<0.05$ compared to baseline; §$P<0.05$ compared to control group.

Not surprisingly, published clinical studies of androgen supplementation in COPD have generally shown modest improvements in muscle mass, but without unequivocal improvements in either muscle strength or endurance. These observations do not take into consideration the additional impact of the adverse events of hypogonadism after AAS cessation. These include negative body composition changes that will further compound and increase the risks of low weight.

Another rationale for testosterone supplementation in men with COPD is that circulating levels are lower than those in healthy young men and those in age-matched control subjects.[238] Van Vliet and coworkers report half of the 78 patients with COPD had low levels of free testosterone, whereas a quarter of the 21 control subjects were hypogonadal.[239] The prevalence of hypogonadism in the control group of Van Vliet and colleagues is lower than the 34 to 40% prevalence of hypogonadism for subjects in their 60s and than the near 70% prevalence for

subjects in their 70s reported in population studies in North America and Europe.[240] Pooling of the data of Van Vliet and colleagues with three other recent studies, there is a 43% overall prevalence of hypogonadism in men with COPD, consistent with the reported range from population studies in North America and Europe.[241] In addition, there is a lack of correlation between testosterone levels and severity of obstruction or with potential causes of hypogonadism specific to patients with COPD, such as hypoxemia or glucocorticoid therapy.

Further, men who have COPD and low testosterone levels do not differ from their eugonadal counterparts in respiratory symptoms, quality of life, respiratory muscle strength, endurance, and exercise capacity.[242] Replacement therapy does not increase exercise capacity or respiratory muscle strength in these patients.[243] Therefore, it is difficult to justify that goals of replacement therapy are to improve these parameters.[244] The issue is whether clinically important functional differences between hypogonadal and eugonadal patients do exist, which could have important therapeutic implications.

Thankfully, the lack of improvement in functionality has tended to temper enthusiasm for anabolic hormone supplementation in COPD. In 2007, the American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) published a systematic, evidence-based review of pulmonary rehabilitation guidelines.[245] The recommendation is current scientific evidence does not support the routine use of anabolic agents in pulmonary rehabilitation for patients with COPD. The recommendation grade, 2C, is their weakest recommendation, finding the strength of evidence is low or very low and it is uncertain if benefits outweigh risks/burdens.

Much more problematic and dangerous is the arrogance and ignorance of these physician investigators. Focusing only on body composition changes that are at most barely significant and without any significant changes in COPD functional measures, researchers propose that reasons for this is AAS doses have been too low and not of a long enough duration.[246] Casaburi et al. state, "It deserves to be stressed that our trial studied short-term effectiveness of testosterone, strength training, and their combination in improving muscle mass and strength. We emphasized that our results, though quite encouraging, deserve further investigation in larger studies of longer duration." Conducting research under either of these conditions will threaten the health and welfare of the subjects. ASIH will occur upon AAS cessation, exposing the individuals to ASIH of a longer duration and greater severity. These studies must cease and desist immediately until there is an accounting for the period of hypogonadism after AAS cessation.

- 7 -

CHRONIC KIDNEY DISEASE HEMODIALYSIS

In 1989, a clinical study using AAS for uremic anemia in male chronic renal failure (hemodialysis) patients, both reported and warned of the period of hypogonadism after AAS cessation.[247] Twenty-three patients who received anabolic steroids showed significantly lower testosterone values than did patients without these steroids. The authors warned that anabolic steroid administration is a possible cause for uremic hypogonadism. Thus, care is important when prescribing these analogues. "Nandrolone decanoate are anabolic steroids prescribed for uremic anemia and those may possibly exacerbate uremic gonadal damage." The adverse effects of AAS demonstrated in these early studies went completely ignored in later studies on identical populations, hemodialysis patients.

In less than a decade, published papers recommending the use of AAS treatment fail to reference, cite, discuss, or mention these early results describing adverse events after AAS cessation. Incredibly, the studies state: "In conclusion, androgen administration has beneficial effects on erythropoiesis, as well as positive anabolic actions in patients under peritoneal dialysis."[248] "The use of Nandrolone decananoate will allow us an acceptable treatment of anemia, as well as a better nutritional condition in elderly patients on dialysis."[249] "Treatment with Nandrolone for six months resulted in a significant increase in lean body mass associated with functional improvement in patients undergoing dialysis."[250]

In a period of less than ten years, publications on AAS prescribing described negative and positive benefits in chronic renal failure (hemodialysis). The latter studies conclusions advocated the use of AAS. The latter studies, however, did not take into account the effect of AAS cessation, ASIH, upon the body's homeostasis. Referencing of the earlier papers warning of the adverse effects upon AAS cessation in similarly affected hemodialysis patients did not occur in any of the latter publications. Additionally, studies ignored obvious clinical signs deserving investigation and explanation. As an added insult to those that have gone before us is the blatant indifference to prior published studies. It is ironic and saddening that this clinical problem published in 1989 concerning hemodialysis patients only to go ignored in recently published studies.

KDOQI (Kidney Disease Outcomes Quality Initiatives), an effort to improve patient outcomes through the development of clinical practice guidelines, defines chronic kidney disease (CKD) according to the presence or absence of markers of kidney damage and the level of kidney function (glomerular filtration rate [GFR]), irrespective of the type of kidney disease (the specific diagnosis) that persist for at least three months. GFR (glomerular filtration rate) is the

best measure of overall kidney function in health and disease. GFR is calculated from a routine blood test, serum creatinine, and the age, sex, and race.[251]

The US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification divides CKD into five stages defined by evidence of kidney damage and level of renal function as measured by GFR, regardless of underlying cause. The term CKD refers to the five stages of kidney disease, the early stages (stages 1 and 2) as well as kidney failure (stage 5). Stage 5 CKD may be described as established renal failure (also called end stage renal failure), and is CKD which has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) will be required to maintain life. Established renal failure is an irreversible, long-term condition.

Data from the third US National Health and Nutrition Examination Survey (NHANES III) suggests that overall 11% of the population have some degree of kidney disease. In the US alone, 20 million adults (1 in 9) have CKD and another 20 million are at increased risk for CKD. Diabetes is the leading risk factor for CKD followed by high blood pressure. The major outcomes of chronic kidney disease, regardless of cause, include progression to kidney failure, which requires dialysis or a kidney transplant to maintain life, complications of decreased kidney function, and cardiovascular disease (CVD).

Anemia is a decrease in red blood cell (RBC) mass. In practice, discovery and quantifying anemia is by the measurement of the RBC count, hemoglobin (Hb) concentration, and hematocrit (Hct). Hemoglobin (the oxygen-carrying protein in the red blood cells) has to be present to ensure adequate oxygenation of all body tissues and organs. Anemia results in a reduced ability of blood to transfer oxygen to the tissues, causing tissue hypoxia. Anemia is an almost-universal complication of renal insufficiency with significant consequences such as fatigue, reduced stamina, decreased cognition, sexual dysfunction, impaired immunity, and diminished quality of life. It also plays a critical role in the development of the structural and functional alterations of the cardiovascular system that are associated with uremia, and contributes to accelerated atherosclerosis.[252]

Early investigations firmly established the stimulatory effects of androgens on erythropoiesis.[253] Diverse studies in the 1970s demonstrated that androgens therapy was associated with favorable effects on anemia in hemodialysis patients.[254] This practice has become in disuse since the synthesis and production of erythropoietin.[255] Erythropoietin or EPO is a hormone produced by the kidney and is the hormone regulating red blood cell production. Erythropoietin is available as a therapeutic agent produced by recombinant DNA technology. Since the introduction of biorecombinant erythropoietin (rHuEPO), most of the anemia in ESRD is corrected, regardless of endogenous erythropoietin levels.[256] Interest in the use of androgens as adjunctive treatment in the management of anemia associated with CKD stems from their use prior to the availability of erythropoiesis stimulating agents (ESAs).

Still not completely understood is the mechanism of action of androgens on erythropoiesis and mechanisms proposed include increased production of endogenous erythropoietin, synergism with ESAs, enhanced sensitivity of erythroid precursors to erythropoietin, increased red cell survival, and a direct effect on erythroid precursors. There is

thus a potential role for androgens in enhancing the effectiveness and reducing the dose requirements of available ESAs.

Investigations have shown that androgens alone are also effective in the treatment of renal anemia. A literature search identified studies, including two RCTs, three cohort studies, and one before and after study. Some studies were retrospective or included a small numbers of patients. Two studies have methodological limitations.[257] The studies were investigating epoetin vs. nandrolone,[258] epoetin vs. epoetin and nandrolone,[259] epoetin and nandrolone (no control group),[260] and nandrolone alone (no control group).[261]

In a before and after study conducted in male (n=9) and female (n=8) patients, Hb (p=0.001) and Hct (p=0.003) levels increased following adjuvant therapy with epoetin (3,000 U/week s.c.) and nandrolone decanoate (100 mg i.m. weekly) for 6 months. When stratified into sex of patients, Hb and Hct levels (both p=0.01) were higher only in female patients.[262]

In a cohort study conducted in male (n=67) and female (n=17) patients, Hb and Hct levels rose (both $P<0.01$) following 6 months therapy with nandrolone decanoate 200-mg i.m. weekly. Although baseline Hb levels were higher in the male patients ($P<0.05$), the increase with respect to baseline levels was similar in both sexes throughout the study. In order to evaluate the influence of other factors, patients were divided into the following: (1) non-responders (Hb increase <1 g/dL with respect to baseline; n=28), (2) mild responders (Hb increase 1–1.9 g/dL with respect to baseline; n=18), (3) good responders (Hb increase 2–2.9 g/dL with respect to baseline; n=25), and (4) excellent responders (Hb increase >2.9 g/dL with respect to baseline; n=13). Only age was significantly associated with response to androgen therapy ($P<0.01$). When the cohort was stratified into ages less than 46 years (n=29), 46–55 years (n=28) and more than 55 years (n=27), only the latter two groups showed improvement in Hb levels (both $P<0.01$) following androgen therapy.[263] In 1996, a 6-month cohort study of hemodialysis patients conducted to compare the effect of 200-mg nandrolone decanoate i.m. once weekly in males over 50 years (n=18) vs. epoetin 6,000 IU a week in male and female patients less than 50 years (n=22) found an increase in Hb levels in both groups (both $P<0.01$).[264]

Hb and Hct levels increased in both treatment groups in a 6-month RCT comparison between rHuEPO and androgens in continuous ambulatory peritoneal dialysis patients. The investigation studied the influence of epoetin initiated at 50 U/kg/week and tailored to target Hb of 11–13 g/dL vs. nandrolone 200 mg i.m. once weekly (both p<0.001) when compared with baseline values. However, these increases in Hb and Hct levels were not significantly different when the treatment groups were compared with each other.[265] Gascón et al. reported similar results.[266] In that study, 33 hemodialysis patients receiving rHuEPO were randomized to either continue this therapy (n = 19) or to stop 15 days before the start of nandrolone decanoate (n = 14). After 6 months, there were no significant differences in the hematological parameters between the two groups.

In a cohort study conducted over 12 weeks in male patients treated with epoetin 6,000 U i.v. 3 times a week (n=7) vs. epoetin 6,000 U i.v. 3 times a week and 100 mg nandrolone decanoate i.m. once a week (n=8), Ballal et al. observed a much greater hematocrit increase in

patients receiving rHuEPO plus nandrolone decanoate than in those receiving rHuEPO alone (from 24.4 to 32.9% vs. 25.3 to 27.4%, respectively, $P<0.001$).[267]

A long-term prospective RCT conducted in predominantly black male and female patients administered with epoetin 4,500 U per week vs. epoetin 4,500 U per week (n=10; 4 men and 6 women) and nandrolone 100 mg i.m. once a week (n=9; 7 men and 2 women) over 26 weeks found a significant increase in Hct in both treatment groups when compared with baseline values (p=0.003 and p=0.001 respectively). The authors found that the use of a combination of low-dose rHuEPO and nandrolone decanoate was associated with a significantly greater increase in hematocrit than the use of rHuEPO alone (8.2 vs. 3.5%, respectively, $P=0.012$).[268]

In a before and after study conducted in male (n=9) and female (n=8) patients, weekly epoetin doses following adjuvant therapy with nandrolone decanoate (100 mg i.m. weekly for 6 months) did not change significantly, either in the overall cohort or when stratified into male and female patients.[269] In a cohort study conducted over 12 weeks in male patients treated with epoetin (6,000 U i.v. three times a week) (n=7) vs. epoetin (6,000 U i.v. three times a week) and nandrolone decanoate 100 mg i.m. once a week (n=8), no difference was observed in epoetin dose between the two treatment groups.[270]

From these studies, there is some evidence of efficacy in that the administration of androgens could reduce the dose of ESA required but the potential side effects make this an outdated approach to anemia management. The National Kidney Foundation does not recommend androgens as an adjunctive therapy to end stage anemia treatment or for erythropoietin resistance in patients with CKD because the adverse effects of androgen therapy appear to outweigh its potential benefits.[271] In people with anemia of CKD, androgens are not an appropriate treatment for anaemia.[272]

The widespread availability of recombinant human erythropoietin for the treatment of anemia associated with chronic renal failure has virtually eliminated the use of nandrolone in dialysis patients in the United States. Nevertheless, in spite of the success of rHuEPO and the parallel disuse of androgenic steroids, interest in the use of androgens, both alone or combined with rHuEPO, in the treatment of renal anaemia has remained alive in several circles. Within the past decade, nandrolone administration recommendations for use in uremic anemia are because of beneficial effects on erythropoiesis as well as positive anabolic actions.

Maintenance dialysis patients encounter multiple catabolic processes and experience a unique form of protein and energy malnutrition characterized by muscle wasting and decreased visceral protein stores. The pathophysiology of muscle wasting in chronic kidney disease clearly is complex, multifactorial, and not fully elucidated. In addition, considerable data exist that as a group, maintenance dialysis patients have low levels of physical function and that both survival and hospitalization rates are directly proportional to physical performance.[273] Abnormalities in muscle function, exercise performance, and physical activity begin in earlier stages of chronic kidney disease and progressively worsen as end stage renal disease (ESRD) ensues.[274]

In the United States, the average life span of a patient entering a long-term dialysis program is less than half that of an age-matched control not receiving dialysis.[275] Although the cause of this discrepancy is probably multifactorial, both malnutrition and reduced muscle mass

are common in dialysis patients.[276] Nutritional markers, such as lean body mass (LBM) and serum albumin, predict outcome in dialysis patients, in whom protein-energy malnutrition is associated with increased morbidity and mortality.

The metabolic effects of human growth hormone (hGH) may improve the nutritional and cardiovascular health of these patients and consequently reduce morbidity and mortality. Anabolic agents, such as human growth hormone, can improve nitrogen balance in patients undergoing dialysis and in other catabolic states. Human growth hormone reduces urea generation and protein catabolic rate in long-term hemodialysis patients in short-term studies.[277] A recent study shows that hGH treatment increases LBM significantly versus placebo.[278]

Anabolic steroids, such as nandrolone decanoate, accomplish some of the same anabolic effects of human growth hormone. Nandrolone and other anabolic steroids have been used by athletes to build muscle mass and enhance weight-lifting performance, and a recent placebo-controlled study shows that supraphysiologic dosages of testosterone resulted in an increase in muscle mass and strength in normal subjects.[279] AAS treatment of hemodialysis patients to improve the nutritional status of dialysis patients might improve mortality outcome. Thus, the rational, logic, and reasoning of the research design using AAS.

Nandrolone decanoate has been the most extensively used of the compounds, and currently available data strongly suggest that this agent is the androgen of choice for ESRD patients. Nandrolone decanoate, 19-nortestosterone, appears almost universally in published literature for the treatment of uremic anemia. Within the past decade, multiple publications describe AAS administration, nandrolone decanoate, in chronic renal failure (hemodialysis) patients for the anabolic effects.

For example, Navarro et al. in a prospective randomized study in peritoneal dialysis patients receiving nandrolone decanoate showed a significant improvement of anthropometric and biochemical nutritional variables when compared with subjects treated with rHuEPO.[280] Navarro et al. in another study concluded androgen administration had beneficial effects on erythropoiesis, as well as positive anabolic actions in patients under peritoneal dialysis.[281] Gascón et al. observed that hemodialysis subjects on nandrolone decanoate had a significant increase in serum creatinine, total protein, and transferrin, along with an improvement of anthropometric parameters.[282] Gascon et al. concluded, "The use of nandrolone decananoate will allow us an acceptable treatment of anemia, as well as a better nutritional condition in elderly patients on dialysis." Teruel et al. found that patients treated with nandrolone decanoate had an increase in dry weight and serum albumin, whereas these parameters did not change in subjects receiving rHuEPO.[283] Other studies using similar research designs also find positive body composition changes.[284]

Johansen et al. (University of California, San Francisco-affiliated dialysis units) in a series of articles stretching from 1999 to 2006 reported the use of nandrolone decanoate is an acceptable treatment of anemia, as well as producing a better nutritional condition in patients on dialysis.

In 1999, Johansen et al. reported nandrolone has beneficial effects on erythropoiesis, as well as positive anabolic actions in patients under peritoneal dialysis.[285] The reported treatment with nandrolone for six months resulted in a significant increase in lean body mass associated with functional improvement in patients undergoing dialysis.

The patients in the nandrolone treated group by the end of the three-month treatment had hypogonadotropic hypogonadism. Total serum testosterone and luteinizing hormone levels decreased significantly in men who received nandrolone but not in men who received placebo. Reported serum testosterone level significantly decreased from 329-ng/dL to 164-ng/dL while luteinizing hormone significantly decreased from 4.4-IU/L to 1.2-IU/L. In addition, one nandrolone recipient complained of a reduction in testicular size.

Hormone Levels in Men at Baseline and After 3 Months of Treatment

**P<0.05	Nandrolone		Placebo	
	Baseline	3 Months	Baseline	3 Months
Total Testosterone, ng/dL	329 (160)	**164 (129)	439 (210)	439 (104)
Luteinizing hormone, IU/L	4.4 (5.0)	**1.2 (2.5)	5.9 (5.1)	6.0 (5.3)
Follicle-stimulating hormone, IU/L	4.4 (2.4)	**0.9 (2.0)	6.4 (5.0)	7.9 (5.0)

Both serum testosterone and luteinizing hormone levels significantly decrease with nandrolone administration. Once again, in a vulnerable population, chronic renal failure, the effects of ASIH are dismissed and ignored that directly affect the primary outcomes of the study. In a later study, involving a larger number of subjects, sex hormone measurements are completely absent.

In 2006, in a 12-week study, male patients received 200 mg nandrolone decanoate weekly.[286] Primary outcomes included change in lean body mass (LBM), quadriceps muscle cross-sectional area, and knee extensor muscle strength. This study reports to be the largest randomized, controlled trial of exercise or anabolic steroid interventions conducted among dialysis patients. Participants, hemodialysis patients, were randomly assigned to one of four treatment groups: (1) nandrolone decanoate, a synthetic testosterone derivative, by weekly intramuscular injection, (2) weekly placebo injections, (3) lower extremity resistance exercise training during dialysis sessions three times per week plus weekly placebo injections, and (4) resistance exercise plus nandrolone injections weekly. Interventions included double-blinded weekly nandrolone decanoate (100 mg for women; 200 mg for men) or placebo injections and lower extremity resistance exercise training for 12 weeks during hemodialysis sessions three times per week using ankle weights.

Primary outcomes included change in lean body mass (LBM) measured by dual-energy x-ray absorptiometry, quadriceps muscle cross-sectional area measured by magnetic resonance imaging, and knee extensor muscle strength. Secondary outcomes included changes in physical performance, self-reported physical functioning, and physical activity.

Patients who received nandrolone decanoate increased their LBM by 3.1 ± 2.2 kg ($P <$ 0.0001). Exercise did not result in a significant increase in LBM. Quadriceps muscle cross-sectional area increased in patients who were assigned to exercise ($P = 0.01$) and to nandrolone ($P < 0.0001$) in an additive manner. Patients who exercised increased their strength in a training-specific fashion, and exercise was associated with an improvement in self-reported physical functioning ($P = 0.04$ compared with nonexercising groups).

The conclusion, "that weekly nandrolone decanoate treatment and lower extremity resistance exercise training during dialysis for 12 wk were safe and well tolerated" did not monitor or measure sex hormones and fails to consider the period after AAS cessation. The study includes the statement, "We previously reported that six mo of treatment with nandrolone decanoate increased LBM and improved walking and stair climbing."[287] In 1999, Johansen et al. reported nandrolone has beneficial effects on erythropoiesis, as well as positive anabolic actions in patients under peritoneal dialysis. The patients in the nandrolone treated group by the end of the three-month treatment had hypogonadotropic hypogonadism. Both serum testosterone and luteinizing hormone levels significantly decrease with nandrolone administration. Thus, the investigators know the effects of nandrolone decanoate administration upon serum sex hormones.

Although side effects were noted in some studies, the authors did not attempt to quantify all of these, none includes discussion of ASIH, and only one includes laboratory assessment of the HPTA. The research design of these studies does not take into consideration that AAS use causes a disruption of the hypothalamic-pituitary-testicular axis, resulting in a state of hypogonadism that after AAS cessation continues for an unknown duration and severity. Documentation in peer-reviewed literature shows AAS prescribing with clinical doses and durations to cause both HPTA suppression and hypogonadism that continues after AAS cessation. None of these published studies noted or referenced the previous work cited above that studied AAS in hemodialysis patients.

In a vulnerable population, chronic renal failure, the effects of ASIH are dismissed and ignored that directly affect the primary outcomes of the study. It is inexcusable for the research design failure to exclude the effects of hypogonadism after AAS cessation. Effects that had they been included would surely negate the significant positive body composition changes found and the proposed and hypothetical benefit of AAS treatment. Extraordinarily unethical and unsound scientific practices in clinical trials places a countless number of vulnerable individuals in harms way.

The clinical trials advocating androgen (nandrolone decanoate) use in CRF are not only endangering the health and welfare of these individuals but the basis for the clinical treatment is upon unsound research design. For those publishing the results of nandrolone decanoate in CRF for anemia and positive body composition changes there is little doubt the studies are done in violation of 45 C.F.R. 46 Protection of Human Research Subjects (“Common Rule”).

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OSTEOPOROSIS & GLUCOCORTICOIDS

The definition of osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis is a common disease associated with aging. Studies have shown that after the age of 30, bone loss commences and significantly increases with age, particularly after age 70.[288] Others have confirmed that bone mineral content and bone density are negatively associated with age at most skeletal sites.[289]

Glucocorticoids belong to the family of compounds called corticosteroids. Corticosteroids are any of the steroid hormones produced by the adrenal cortex except for the sex hormones. These include the mineralocorticoids (aldosterone) and glucocorticoids (cortisol). Glucocorticoids affect metabolism and have anti-inflammatory and immunosuppressive effects. They may be naturally produced (hormones) or synthetic (drugs). Cortisol (or hydrocortisone) is the most important human glucocorticoid.

In addition to their physiologic importance, glucocorticoids are also among the most frequently used drugs, and often prescribed for their anti-inflammatory and immunosuppressive properties. National estimates indicate that 0.5–0.9% of the total adult population are using oral corticosteroids.[290] Among patients with chronic medical disorders, glucocorticoids are among the most widely used drugs. Glucocorticoids continue to be the first-line therapy for the most serious inflammatory disorders, including rheumatologic, pulmonary (chronic obstructive pulmonary disease), renal, and neurological disorders.

Glucocorticoid therapy has frequent significant adverse effects. The adverse effects of corticosteroids include new-onset diabetes, hyperlipidemia, hypertension, growth retardation, accelerated bone loss, weight gain, avascular necrosis, cataracts, cosmetic changes, depression, psychotic behavior, and others.[291] Long-term administration of corticosteroids is associated with numerous adverse effects that lead to increased patient morbidity and mortality,[292] particularly muscle loss and bone loss, which may decrease quality of life through frailty, falls, and fractures.

A major health complication of the elderly is the increased risk of falls and fractures. Falls, and the resulting fractures, are a major cause of disability, morbidity, and mortality in the elderly. These falls account for numerous injuries and hospitalizations and a substantial health care burden.[293] The Centers for Disease Controls National Center for Injury Prevention and

Control reported that from 1996-1998 falls were the third leading cause of unintentional death in the United States (35,745 deaths). Injury and mortality due to fractures and falls can be attributed to the loss in lean muscle, functional strength, bone loss, balance, or a combination of these variables.

A debilitating consequence of chronic corticosteroids is glucocorticoid-induced osteoporosis (GIOP). Bone loss significantly increases fracture risk.[294] Fracture of the spine may further worsen respiratory function,[295] and hip fracture is associated with strikingly increased mortality and morbidity, particularly in men.[296]

In glucocorticoid-induced osteoporosis, the risk of fractures exceeds the risk of reduced bone mineral density. These glucocorticoid effects are related to the dose and duration of therapy, although prolonged exposure to modest, frequently considered physiological doses of glucocorticoids may also be detrimental and have been shown to increase fracture risk.[297] The largest reductions in bone mass resulting from GIOP occur during the first 6 months of treatment, and the risk of fracture increases rapidly within the first 3 months of glucocorticoid therapy.[298]

There are a number of comprehensive reviews on the pathogenesis of GIOP.[299] Several aspects of GIOP help explain the severity of GIOP and the rationale for various preventive and therapeutic maneuvers. Bone undergoes a remodeling cycle in which osteoclasts first resorb bone over a period of about 2 weeks. Thereafter osteoblasts appear and fill in the resorbed area over a 3- to 4-month period. In GIOP, while resorption may or may not be increased, bone formation is greatly diminished. This particular mechanism may be the reason that GIOP can lead so rapidly to bone loss and increased fracture risk.

Other mechanisms are also important. Glucocorticoids cause increased urinary calcium excretion and decreased intestinal absorption of calcium, possibly leading to secondary hyperparathyroidism. This results in loss of bone mineral. In addition, the general catabolic effects of glucocorticoids cause decrements of bone matrix and muscle.

Glucocorticoid therapy may affect pituitary gonadotropin secretion, causing a functional hypogonadism in men.[300] Glucocorticoid therapy results in decreased serum testosterone levels[301] because of combined effects on reduced GnRH secretion and a direct effect on testosterone production from the testes.[302] Androgen treatment can restore deficits in bone mineral density (BMD) in hypogonadal men.[303] In men made hypogonadal by glucocorticoid therapy, it makes intuitive sense to replace androgens.

In the early 1940s, Albright and Reifenstein were among the first to refer to the antiosteoporotic and anabolic properties of androgens.[304] Male hypogonadism can be due to a variety of diseases, which may all have a specific impact on skeletal integrity. Nevertheless, comparative data suggest similar impairment in bone density in men with different etiologies of hypogonadism, suggesting that hypogonadism per se and not the primary disease entity is responsible for the bone loss.[305] In addition to the decline in bone density, hypogonadal-induced changes in body composition, including decreased lean body mass, may further enhance fracture risk.[306] Androgen replacement therapy in hypogonadal men[307] as well as pharmacological androgen therapy in eugonadal men[308] increases muscle mass and strength. The potential benefits

of testosterone replacement in indications other than overt hypogonadism are not well established.

Based upon this premise, a published study reported on the effects of AAS treatment in opposing some of the catabolic glucocorticoid effects on muscle and bone and measure changes in functional status (i.e. muscle strength, quality of life).[309] By using equivalent doses of testosterone and its minimally aromatizable analog, nandrolone (19-nortestosterone),[310] the study aim was to determine the importance for any potential therapeutic effects of androgen therapy. This work was supported in part by Organon (Australia) Pty. Ltd., manufacturer of nandrolone.

The study tested the effect of two androgens, testosterone and nandrolone, on muscle mass (dual x-ray absorptiometry), muscle strength (knee flexion and extension by isokinetic dynamometry), bone mineral density (BMD), and quality of life (Qualeffo-41 questionnaire) in 51 men on a mean daily prednisone dose of 12.6±2.2 mg. Randomization, double blind, of subjects was to three groups: (1) placebo, (2) nandrolone decanoate (200 mg), and (3) testosterone (200 mg mixed esters) by intramuscular injection every two weeks for 12 months.

At 12 months, both androgens significantly increased muscle mass (mean change from baseline +3.5%, +5.8%, and -0.9% in testosterone, nandrolone, and placebo groups, respectively, $P<0.0001$) and muscle strength ($P<0.05$). Lumbar spine BMD increased significantly only in men treated with testosterone (4.7±1.1%, $P<0.01$). There was no significant change in hip or total body BMD. Testosterone, but not nandrolone or placebo, improved overall quality of life ($P<0.001$). The results, according to the authors, suggest that androgen therapy may have a role in ameliorating adverse effects of glucocorticoid therapy such as muscle and bone loss.

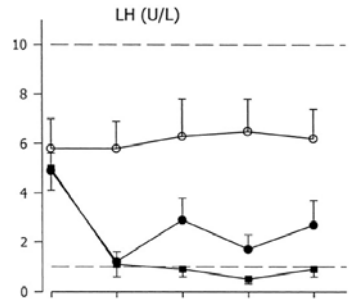
At entry into the study, 18 men (six in each treatment group) had a testosterone level below the lower limit of the eugonadal reference range (<11 nmol/liter) and another 16 (seven, five, and four men in testosterone, nandrolone, and placebo groups, respectively) had a testosterone level in the low-normal range (11–15 nmol/liter). The table below is the baseline characteristics (mean ± SEM) of men randomized to treatment with testosterone, nandrolone, or placebo. Normal ranges for hormones: total testosterone, 11–35 nmol/liter; LH, 1–10 IU/liter; FSH, 1.0–8.5 IU/liter.

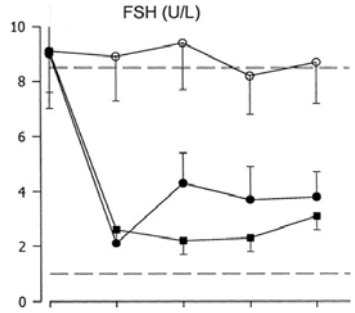
Treatment group	Testosterone	Nandrolone	Placebo
Number	18	17	16
Age (yr)	58.7 ± 4.9	62.7 ± 4.2	59.9 ± 4.0
Primary disease			
Respiratory disease	10	11	10
Immune or inflammatory disease	8	6	6
Hormones and biochemistry			
Total testosterone (nmol/liter)	13.8 ± 0.4	13.2 ± 0.3	15.7 ± 0.5
LH (IU/liter)	4.9 ± 0.7	5.0 ± 0.9	5.8 ± 1.2
FSH (IU/liter)	9.0 ± 2.5	9.1 ± 2.1	9.1 ± 1.5

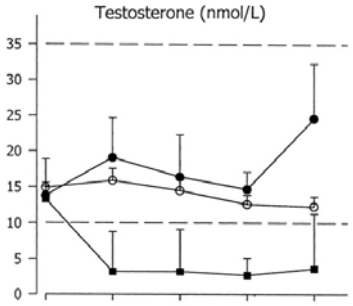
With nandrolone treatment, plasma total and free testosterone concentrations were markedly suppressed ($P<0.001$), but there was no change with time in the placebo group. Mean plasma total testosterone remained within the eugonadal reference range for both the testosterone and placebo treatment groups. There was significant suppression of both LH and FSH serum levels with testosterone and nandrolone but were unchanged with placebo.

It is clear from the study data that hypogonadism is present in the testosterone and nandrolone treatment groups. In the nandrolone treatment group, the significant decrease in LH and testosterone levels is consistent with hypogonadotropic hypogonadism. Due to testosterone administration, there is a significant decrease in LH but not serum testosterone in the testosterone treatment group. Representation of the data is in the figure below. It is inarguable that ASIH will occur after AAS cessation.

Serum levels (mean ± SEM) of testosterone, free testosterone, LH, and FSH in men treated with testosterone (•), nandrolone (■), or placebo (○). Dashed bars represent the normal ranges for adult men.







In 2006, Tracz et al. published the report, "Testosterone Use in Men and Its Effects on Bone Health. A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials."[311] The analysis included eight trials enrolling 365 patients, including the study above.[312] The study is a systematic review and meta-analysis of randomized placebo-controlled trials in men to estimate the effect of testosterone use on bone health outcomes.

The study conclusions state, "Intramuscular testosterone moderately increased lumbar bone density in men; the results on femoral neck bone density are inconclusive. Without bone fracture data, the available trials offer weak and indirect inferences about the clinical efficacy of testosterone on osteoporosis prevention and treatment in men."

Trial characteristics found were all but two trials enrolled patients with low normal and normal testosterone levels at baseline. Although, a review of the study data for the mean testosterone level at baseline do not indicate hypogonadal levels. Significantly, test for interaction between treatment effect and on-trial testosterone levels was not possible because reporting of testosterone levels during the trial was not consistent across trials. No trials measured or reported the effect of testosterone on fractures.

Importantly, a stated limitation of the power of this study was the number of discontinuations, most of which were due to adverse events occurring in men with concurrent chronic illnesses and significant comorbidity. Thus, pointing out and emphasizing that AAS treatment is of a limited duration. Upon AAS cessation, a period of hypogonadism will ensue of unknown severity and duration. ASIH will occur in individuals with comorbid conditions that place them in a greater state of ill health, resulting in a probable increase in morbidity and mortality.

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SARCOPENIA

Sarcopenia is a word coined from Greek by Rosenberg in 1988 from *sarx* meaning flesh and *penia* meaning loss.[313] Sarcopenia is the progressive, age-related decline in muscle mass and strength. A number of anatomic and physiological changes characterize aging in humans, including the progressive loss of muscle mass and strength (sarcopenia), which contributes to the sequential loss of voluntary skeletal muscle strength and physical function.[314] There is an approximate 33% reduction in muscle mass between the ages of 30 and 80 years, and this loss increases to 1% per year after the age of 70 years.[315] This leads to diminished strength and function. Isometric and dynamic maximal voluntary strength of the quadriceps muscles decreases after the age of 50 years and there is an approx 30% decrease in strength between 50 and 70 years.[316]

The age and sex-adjusted prevalence of sarcopenia varies from 6% to 24%, depending on the definition and measure of muscle mass used.[317] Baumgartner and colleagues in the New Mexico Elder Health Survey 1993-1995 assessed the epidemiology of sarcopenia. When they compared an elderly population of Hispanics and non-Hispanic whites to a reference standard young adult population, sarcopenia (appendicular muscle mass less than two standard deviations below the mean of the young adult reference) prevalence was found to be 13-24% of subjects under 70 years. When they expanded their sample to subjects over 80 years of age the prevalence increased to >50%. In this study, sarcopenia was significantly associated with self-reported physical disability.

Sarcopenia has been associated with disability in both men and women.[318] The Framingham Disability Study found that the ability to perform heavy household work, walk one half mile, and climb stairs declined with age and that participants aged 75–84 were more likely to require help with activities of daily living.[319] Muscle weakness is a common feature in elderly subjects who fall, a common cause of accidental injury and fracture in the elderly.[320] The likelihood of falling is increased by the age-related development of sarcopenia, weakness, and impairments in physical performance.[321] Many elderly persons fall each year; repetitive falls are common, and the likelihood of falling increases quickly with advancing age.

The impact of sarcopenia over an entire population is very significant. Sarcopenia impacts lean body mass, muscular strength, aerobic capacity, balance, metabolism, bone density, and immune function. It is not surprising that all-cause mortality is increased in elderly persons

exhibiting one or more of the effects of sarcopenia.[322] Studies have found that grip strength is a strong predictor of all-cause mortality.[323] Limitations of these studies include the unclear differentiation between strength, muscle mass and physical activity in the predictive benefits of grip strength on all-cause mortality but the relationship is still significant. Another study investigating risk factors in older adults demonstrated that low body weight, lack of regular exercise, and difficulty with 2 or 3 or more of instrumental activities of daily living were associated with increased mortality.[324] Improving lean muscle mass and strength would directly influence all three risk factors from this study. Leg extensor power has been associated with better performance in chair rising, stair climbing, and walking in older community-dwelling adults.[325]

Proven treatments to combat the progressive loss of muscle mass and strength with ageing include improved diet, nutrition counseling, and progressive resistance training. Dietary counseling stressing the need for additional protein intake to account for the increased rate of protein synthesis is important when treating sarcopenia. A progressive resistance training routine focusing on compound exercises utilizing multiple muscle systems and progressive skeletal loading is important for improved bone mineral density, lean muscle mass, strength, and metabolism.

In 1970, Forbes concluded that both age and sex should be considered in determining drug dosages and nutritional requirements based on the decline in lean body mass.[326] Bortz, in 1982, commented that disuse of muscle resulted in loss of lean body mass.[327] Gallagher and colleagues found that gender greatly influenced muscle mass and that, with age, men experience a decline in muscle mass almost twice that of women.[328] Theoretically, predictors of a decline in muscle mass and muscle strength and their treatment should decrease morbidity and mortality.

In 1944, a paper accurately described symptoms, diagnosis, and treatment of the male climacteric by testosterone replacement but not by placebo, in men suffering from an age-associated decline in testosterone concentrations.[329] Since that time, various terms, other than the male climacteric, have been applied to the hormonal changes of male aging. PADAM is the mnemonic for partial androgen deficiency in the aging male. Andropause, it appears has taken hold as evidenced by its use in the major and popular endocrinology texts.[330]

For many years, there was considerable controversy over whether serum total testosterone levels were lower in healthy older men; it was argued that older men had lower testosterone levels because of the confounding influence of chronic illness and medications. A number of cross-sectional studies have reported a decline in total testosterone with ageing. After accounting for the potential confounding factors such as time of sampling, concomitant illness and medications, and technical issues related to hormone assays, serum total testosterone levels are lower in older men in comparison to younger men. Recent longitudinal studies of normal men have verified the age-related decline in serum testosterone levels.

Examined changes over time have demonstrated a decrease in total testosterone and an increase in sex hormone binding globulin (SHBG) levels.[331] There is general agreement that total testosterone levels and testosterone production rates are lower in older men compared with young healthy men. By the third decade (20-30 years of age), the mean serum testosterone level

generally decreases by 1% to 2% per year. In the normal aging male, Leydig cell function declines with age as shown by a decrease of approximately one-third of total testosterone levels between the ages of 20-30 and 70-80. Approximately 20% of men over 60, 30% over 70 and 50% over 80 yr of age, had total testosterone levels below the lower level of normal for young adult males.

The aging process alters the circadian rhythm in testosterone production normally seen in men, and the mean 24-hour testosterone levels are lower in elderly men. The normal diurnal testosterone cycle generates peak testosterone levels in the morning with an evening nadir. In elderly men, however, testosterone levels fail to increase in the morning. Instead, these men maintain constant testosterone levels throughout the day.[332]

Testosterone and its metabolites play a crucial role in the health of the male. This decline may contribute to a multitude of physiological and psychological changes associated with ageing in men. This decline is associated with alterations in body composition (decrease in muscle mass and increase in fat mass); fatigue (diminished energy), muscle strength and physical function, reduced sexual function (sexual drive and activity), depressed mood and well-being, decreased cognitive function (memory and concentration), and bone mass.[333]

The contribution of age-associated hormonal alterations to these adverse health consequences is unclear. Multiple studies have demonstrated a decrease in serum testosterone levels in men with age. The similarity of changes in muscle composition between castrate animals, hypogonadal men, and aging men suggests a role for relative hypogonadism in the decline of muscle composition/performance and the increase in adipose stores in the elderly.[334] Thus, reductions in muscle mass, strength, and physical performance, and a resultant increase in fall risk, are prominent among the postulated effects of age-related declines in androgen levels.[335] Free testosterone, physical activity, cardiovascular disease, and insulin-like growth factor-1 (IGF-1) are significant predictors of muscle mass in men.[336]

The importance of these changes remains controversial, but modifications in testosterone levels have been postulated to underlie, in part, the occurrence of adverse events that accompany male aging. Testosterone affects many organs and beside its androgenic (masculinizing) actions, the hormone exhibits powerful anabolic properties. These anabolic effects are manifested in an increased protein synthesis and decreased protein catabolism, a larger muscle mass and an increased skeletal maturation and mineralization. In addition, testosterone induces a loss of subcutaneous fat. The anabolic properties of the androgens were reported already in 1935 and clinical studies in the 1950's showed that testosterone administration increased muscle mass.[337] This hypothesis has received widespread attention, and the number of men treated with testosterone has increased rapidly.[338]

There have been several studies evaluating the effects of testosterone replacement on body composition in elderly men. These studies have included subjects with normal serum testosterone values, in order to address the hypothesis that raising levels into the midrange of younger men may have beneficial effects on body composition. Studies of testosterone replacement of older men with low testosterone levels have been shown to increase fat-free mass, decrease body fat, and increase grip strength.[339]

Published literature includes the use of anabolic steroids to improve measures of body composition in sarcopenia. Published studies on the oral anabolic steroids oxymetholone, oxandrolone, and testosterone undecanoate draw conclusions that treatment produces positive anabolic, body composition, changes that might be beneficial for the age related loss of muscle mass and strength. There are, however, no long-term studies demonstrating an effect on either morbidity or mortality.

Published literature has come to include investigations using AAS for their anabolic properties as an added treatment modality. Numerous studies publish the results of the positive anabolic improvements in body composition disregarding the period after AAS cessation. ASIH will negate the positive body composition benefits but impose upon the patient the additional signs and symptoms of hypogonadism. With no guarantee for HPTA normalization and no consideration of caring physicians for ASIH, the patient is in a state of health worse than prior to AAS administration.

A more alarming concern is hypogonadism compounded with the effects of ageing or sarcopenia. The combined effects of ageing or sarcopenia and hypogonadism on lean body mass, muscular strength, bone density, metabolism, aerobic capacity, etc. will only increase morbidity and mortality. A eugonadal population that is experiencing muscle loss due to aging cannot afford to exasperate the situation by becoming hypogonadal. Unfortunately, AAS prescribing in the elderly with no attention to ASIH are to be of no benefit, impose unnecessary costs, expose the patient to hypogonadism signs and symptoms, and endanger their health and welfare.

In 2003, a study published the effects of oxymetholone on muscle and metabolism in older, community-dwelling men.[340] The study was a collaborative effort that included the Departments of Medicine, Radiology, and Biokinesiology, Keck School of Medicine, University of Southern California and Division of Endocrinology, Metabolism, and Molecular Medicine, Charles Drew University School of Medicine, Los Angeles, California. Partial support funding was by a grant-in-aid from Unimed Pharmaceuticals, manufacturers of oxymetholone.[341]

The study was a two-center, investigator-initiated, dose ranging, double blind, placebo-controlled trial. Randomization of 31 men 65-80 years of age were to placebo, 50 mg oxymetholone, or 100 mg oxymetholone daily for twelve weeks. To achieve blinding, the subjects received two placebo tablets, one placebo plus one 50-mg oxymetholone tablet, or two 50-mg oxymetholone tablets. Adherence was monitored by pill counting at each study visit. The study was to determine whether oxymetholone increases lean body mass (LBM) and skeletal muscle strength in older persons.

Oxymetholone treatment with 50 and 100 mg/daily increased LBM (kg) by 3.3 and 4.2, respectively. Trunk fat (kg) decreased by 1.7 and 2.2, respectively. Relative increases in 1-repetition maximum strength for biaxial chest press and lat pull-down in the treatment groups were significantly different from the change for the placebo group. Thus, oxymetholone improved LBM and maximal voluntary muscle strength and decreased fat mass in older men.

Fasting insulin concentrations and derived indexes of insulin sensitivity did not change significantly within treatment groups, nor were there differences between these groups. However,

these conclusions disregard and dismiss the effects of hypogonadism after AAS cessation. Hypogonadism adversely affects insulin sensitivity. This effect, which increases the risk of adverse cardiovascular events, is avoided by not discussing or investigating the period of hypogonadism after AAS cessation.

In this particular study, liver transaminases increased significantly and HDL-cholesterol (good cholesterol) decreased significantly with oxymetholone treatment. A factor often mentioned in any discussion of AAS is the negative effects upon liver function and cholesterol. These are critical and important for the point that these drugs have limited treatment duration and AAS cessation will occur at some point. AAS cessation will begin a period of ASIH of unknown duration and severity.

Serum luteinizing hormone decreased in 50 mg/day and 100 mg/day oxymetholone treatment groups after twelve weeks of study therapy, which were both significantly different from the changes observed in the placebo group. The authors noted, "Oxymetholone administration was associated with decreases in serum LH . . . concentrations. Therefore, at the doses of oxymetholone that are used for anabolic applications, this compound has significant androgenic activity at the hypothalamic-pituitary level." It is clear is the investigators are fully aware that a period of hypogonadism will ensue after AAS cessation. It is also clear that this will adversely affect their results and conclusions.

The investigators include within the METHODS section for Safety Monitoring, "We did not test for total and free testosterone levels at the end of the 12-wk treatment period, because semisynthetic androgens including oxymetholone cross-react in these assays for testosterone." This claim is clearly a specious argument for what in reality is a cover-up for something else. Of all of the statements within this published study, this statement is clearly indicative of questionable research practices that crossover to scientific misconduct.

The reasons for the proposed misconduct are many and discussed in the following chapter.[342] Briefly, a number of reasons standout immediately for the bizarre and ridiculous nature of the claim. First, there is an absence of any citations in support of their problem of cross reactivity of semisynthetic androgens in RIA of serum testosterone. Second, published literature by the same investigators claiming cross-reactivity and serum oxandrolone concentrations demonstrate a pattern. Of note is that only in publications by these investigators is there a claim made for an inability to measure serum testosterone in the presence of semisynthetic androgens. The explanation that cross reactivity with semisynthetic androgens lead to the inability to measure serum testosterone is not present in any other peer-reviewed publication with an AAS in a clinical study. This pattern for the inability to measure serum testosterone in the presence of semisynthetic androgens in clinical situations where there is a significant decrease of serum testosterone levels is suspiciously convenient.

Third, not only is their no published literature in support of the supposed cross reactivity, the published literature demonstrates the exact opposite. Published literature demonstrates the ability to measure testosterone in the presence of oxymetholone. Fourth, RIA manufacturer specifications for cross reactivity concerns do not include oxymetholone.

Fifth, the most revealing for ulterior motives and purposes of the investigators is the drug, itself. Discussed elsewhere, oral AAS have a short half-life.[343] In fact, an almost universal generalization is all oral medications have short half-lives. This is the reason why these medicines need to be taken on a daily, if not more frequently, basis. The pharmacokinetic parameters in healthy volunteers of the oral administration of 50-mg oxymetholone are C(max) and T(max) of 18.8-ng/ml and 3.5-hours (2.75-4.00), respectively; 10 hours posttreatment level 4.0-ng/ml; and elimination half-life of 8.0 hours.[344] Within 24 hours of the last oral dose the serum oxymetholone concentration will be very small and even at a cross reactivity of 100%, the contribution to the serum testosterone will be insignificant. These investigators have control over the appointments, blood draws, etc. and their claim of semisynthetic androgens interfering with the testosterone assay is the extreme height of arrogance.

Often data from a single research protocol is presented in various forms through different articles. Bhasin and colleagues did just this regarding the investigation of oxandrolone administration in elderly men. In 2004, a study (STUDY 1) published the treatment with oxandrolone and the durability of effects (body composition changes: lean body mass and fat mass) in older men.[345] Also in 2004, these same investigators reported (STUDY 2) on the effects of androgen therapy on adipose tissue and metabolism in older men.[346] In 2005, a study published (STUDY 3) on six-week improvements in muscle mass and strength during androgen, oxandrolone, therapy in older men came from the same authors and institutions.[347]

Support for the studies was identical and identified by NIH Grant GCRC MOI-RR-00043 and a grant-in-aid from Savient Pharmaceuticals, Inc., manufacturer of oxandrolone. The studies are collaborative efforts that include some or all of the following institutions: Division of Infectious Diseases, Department of Medicine, General Clinical Research Center, and Department of Radiology, Keck School of Medicine; Department of Biokinesiology and Physical Therapy, University of Southern California; Divisions of Metabolism, Endocrinology and Lipid Research and Cell Biology and Physiology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri.

That the three published studies are from the same set of data becomes obvious upon comparison for the baseline characteristics of the study population. The study groups control and intervention (oxandrolone) have identical values for their mean, standard deviation, and significance level (*P* value) for the metabolic and physical parameters, including total testosterone and luteinizing hormone.[348] The chance of this occurring and being separate research data is infinitesimal, well beyond an order of a 10^9 (billion) magnitude. The ethics of publication are not the focus of this book and any discussion would serve only to distract from the book's purpose in exposing AAS questionable research practices.

Randomization in each study is thirty-two healthy older men to receive (1) oxandrolone (20 mg/daily) or (2) placebo for 12 weeks. Body composition, lower extremity muscle volume, and muscle strength evaluation measurements were at intervals from baseline. Depending on the study, these were at week 6, week 12, or week 24. Week 24 is 12 weeks after oxandrolone treatment discontinuation.

STUDY 1, at week 12, oxandrolone significantly increased LBM, total body water, and proximal thigh muscle area. Oxandrolone significantly increased 1-repetition maximum strength for leg press, leg flexion, chest press, and latissimus pull-down exercises. Oxandrolone significantly reduced total and trunk fat (kg).

STUDY 1, twelve weeks after oxandrolone discontinuation at week 24, the increments in LBM and muscle strength was no longer different from baseline. Thus, treatment with oxandrolone for 12 weeks induced improvements in LBM, muscle area, and strength that were lost 12 weeks after oxandrolone discontinuation. However, the decreases in total and trunk fat were sustained although decreased.

Not surprisingly, STUDY 2 reported on the effects of oxandrolone on regional fat compartments and markers of metabolism. Oxandrolone significantly reduced total and trunk fat than the changes with placebo. Twelve weeks after discontinuing oxandrolone, the reductions in total, trunk, and extremity fat were largely sustained.

STUDY 2 includes a marker of insulin sensitivity significantly improved with oxandrolone at study week 12. Androgen therapy, therefore, produced significant and durable reductions in regional abdominal and peripheral adipose tissue that were associated with improvements in estimates of insulin sensitivity. The authors fail to mention or allude that the after AAS cessation, induced hypogonadism studies conclusively demonstrate adverse insulin sensitivity changes consistent with an increase in cardiovascular risk. In 2007, an induced hypogonadism study demonstrates the increase risk of fatal myocardial infarction.[349]

STUDY 3 was to assess the early effects of a potent anabolic androgen on muscle mass and strength, lower extremity power, and functional performance in older men. At week 6, oxandrolone significantly increased LBM, total body water, and proximal thigh muscle area. Oxandrolone significantly increased 1-repetition maximum strength for leg press, leg flexion, chest press, and latissimus pull-down exercises. The article comments that these improvements were 90% of those seen by week 12.

It is inarguable the data for this study is from STUDY 1. This report is nothing more than a publication on a subset of data from STUDY 1. The authors "[p]reviously reported that 12 weeks of treatment with oxandrolone, a potent anabolic androgen, significantly increased LBM and muscle strength in older men." However, the authors also state, "These gains [LBM and muscle strength] were almost entirely lost 12 weeks after discontinuing treatment . . . ." The use and interpretation of the term almost, at best, is misleading. The authors, themselves, in the abstract state, "Twelve weeks after oxandrolone was discontinued (week 24), the increments in LBM and muscle strength were no longer different from baseline."

Despite full knowledge that these anabolic improvements disappear 12 weeks after drug discontinuation, the article comments that this treatment, 6-weeks, might be beneficial to vulnerable populations that include those with "physical limitations, frailty, or catabolic illness and associated muscle wasting . . . ."[350] With full awareness that their prior study reported on the anabolic improvements in 12 weeks the authors "[b]elieve that this is the first study to report significant improvements in muscle mass and strength in both the upper and lower extremities as

early as 6 weeks after treatment was initiated." Moreover, the prior study reported on the loss of anabolic improvements in 12 weeks after oxandrolone cessation, these same investigators now recommend the use of the drug in a vulnerable population. Not only do these subjects face the loss of anabolic improvements but the additional signs and symptoms of hypogonadism.

In STUDY 3, the authors "[suggest] that prolonged therapy with an anabolic androgen would be necessary to sustain these benefits." This bold statement is contrary and counterintuitive to the study results that lean body mass and strength gains after 12 weeks of anabolic steroid, oxandrolone, treatment are lost 12 weeks after treatment discontinuation. The authors never address, discuss, or propose the possible physiological process responsible for the loss of anabolic improvements. Instead, they offer the suggestion "[t]hat prolonged therapy with an anabolic androgen would be necessary to sustain these benefits" without a hint for the loss. This is irresponsible, dangerous, and arrogant. An arrogance that hopes to dismiss and ignore any argument the physiological process responsible for the loss above is ASIH.

STUDY 1 "[d]id not measure testosterone levels at week 12 because semisynthetic androgens, including oxandrolone, cross-react in these testosterone assays" and "[o]nly measured serum testosterone levels at baseline and week 24." STUDY 2 did not include a reference to serum hormone measurements. STUDY 3 "[d]id not measure testosterone levels at study week 6 or 12 because semisynthetic androgens, including oxandrolone, cross-react in testosterone assays."

These authors state that serum testosterone measurements are not done due to cross reactivity concerns. Recall, these are the investigators that oxymetholone administration lead to the inability to measure serum testosterone for the same reasons. Since there is no further discussion elsewhere, it is noteworthy to comment on the claim that no testosterone measurement was done due to cross reactivity with semisynthetic androgens. A brief discussion on oxandrolone pharmacokinetics reveals the absurdity of the argument put forth that cross reactivity issues cause testosterone measurement to be inaccurate and thus clinically unreliable.

Oxandrolone pharmacokinetics[351] includes Tmax 1.1 hours. The absorption of oxandrolone from the gastrointestinal tract is rapid and complete with peak blood levels occurring between 45 and 90 minutes (Tmax) after oral administration. The maximum plasma concentration of 41.7-ng/dL was observed between 30 and 90 min following oral ingestion of a 10-mg dose. Oral anabolic steroids, including oxandrolone, have a short half-life. Distribution half-life (t1/2 α) 0.55 hour, distribution half-life is the amount of time it takes for half of the drug to be distributed throughout the body. Elimination half-life (t1/2 ß) 9.4 hours, elimination half-life (t1/2 ß) is the time taken for plasma concentration to reduce by 50%. After four half-lives, elimination is 94% complete. Volume of distribution (Vd) is 578 mL/kg.

STUDY 1, STUDY 2, and STUDY 3 (all the same study) administrated 10 mg oxandrolone twice daily. If there was 100% cross reactivity and the blood sample drawn within 30-90 minutes of administration the maximum oxandrolone concentration contribution to the serum total testosterone is 41.7-ng/dL. If there was 100% cross reactivity and the blood sample drawn anytime thereafter, the oxandrolone concentration contribution to the serum total testosterone is less.

In the elegant study by Sheffield-Moore et al. demonstrating that short-term oxandrolone administration stimulates net muscle protein synthesis in young men, the hormone analysis methodology included oxandrolone measurement.[352] Six healthy men were studied before and after taking a daily dose of oral oxandrolone (15 mg/day) at 2100 hours for 5 days. Serum oxandrolone concentrations on day 3 (1.9±0.4-ng/dL) and day 5 (2.2±0.3-ng/dL) of oxandrolone administration, measured 10 hours after each evening's oral dose (2100 hours or 9 PM), remained steady. By 18 hours posttreatment on day 5, serum oxandrolone levels were markedly reduced (0.48±0.06-ng/dL) compared to day 3 or day 5 10-hour values.

In the Sheffield-Moore study, the oxandrolone dose was 15-mg once daily at 2100 hours, with an approximate serum oxandrolone concentration 10 hours after an evening dose of 2-ng/dL. It is inconceivable that the investigators could not withhold the morning dose or instruct the patient not to take their morning dose. Nevertheless, even more highly suspicious and circumspect is serum oxandrolone levels are insignificant within 24 hours after its last administration. There is no, none, plausible reason the investigators could not measure serum testosterone shortly after oxandrolone treatment discontinuation.

The failure of the investigators is more troubling because of the following. STUDY 1 methods state, "Total testosterone concentration (ng/dl) was measured . . . by using Diagnostic Products Coat-A-Count at baseline and week 24, 12 wk after the oxandrolone intervention was completed." STUDY 2 methods include, "The serum testosterone concentration was measured . . . using Coat-A-Count (Diagnostic Products Corp., Los Angeles, CA)." STUDY 3 did not state the methodology for testosterone assay. The expectation is for identical assay systems since the publications are from the same data set.

In 1999, two studies reported on the use of oxandrolone.[353] One of the studies is that by Sheffield-Moore et al. Both studies include measurement of testosterone during the administration period of oxandrolone. These investigators found no problems or concerns for measuring serum testosterone in the presence of oxandrolone administration.

Most important and relevant is the studies utilize the identical testosterone assay system. Serum testosterone measurement used a commercial RIA kit [Coat-A-Count] by Diagnostic Products Corporation, Los Angeles, California. The identical testosterone assay system is used for all of the studies.

Commercial assay kits using unextracted serum or plasma and a ^{125}I-labeled testosterone tracer with solid phase separation methods are technically easy to use, precise, relatively inexpensive, and sufficiently accurate for most purposes.[354] A comparison of commercially available RIA kits found the Diagnostic Products Corporation (DPC) RIA to be the most accurate and was not significantly different when compared with liquid chromatography-tandem mass spectrometry (LC-MSMS).[355] The study found that only DPC-RIA gave serum testosterone levels that were NOT significantly different from gas source mass spectrometry (GS-MS). The DPC-RIA (DPC-Coat-a-Count) is the most common RIA used in hospital or reference laboratories and appears to show the best agreement with serum testosterone values measured in male serum by LC-MSMS.

These latter investigators found no problems or concerns for measuring serum testosterone in the presence of oxandrolone administration. The Coat-A-Count (Diagnostic Products Corp., Los Angeles, CA) RIA serum testosterone assay system includes cross reactivity for a number of drugs. Dihydrotestosterone (DHT) has a 3% cross reactivity. Other cross reactivities of AAS not present endogenously includes 1.7% for methyltestosterone and 20% for nandrolone. However, even at 20% cross reactivity and blood drawn within 30-90 minutes after oxandrolone administration equals a maximum interference of 9-ng/dL (20% X Tmax 41.7-ng/dL). This is using numbers so outlandish and ridiculous that the reason not to measure serum testosterone is certainly suspect.

What is more is that the serum testosterone measurements appear within their articles. Sheffield-Moore et al. found total serum testosterone concentrations by day 5 significantly reduced below day 0 and day 3 values. In the other study, both groups received testosterone enanthate so the oxandrolone effects could be isolated. Thus, direct serum testosterone did not allow an indication for HPTA suppression. However, an indirect measurement of endogenous testosterone production found this significantly decreased and a marker of HPTA suppression. In addition, in another study using a different assay system found serum testosterone significantly reduced with oxandrolone administration.[356]

The investigators include in their study, change in safety measures for LH after 12 weeks of study therapy. All three studies found significant decrease in serum luteinizing hormone (LH). STUDY 1 found "a trend toward a greater decline in LH levels with oxandrolone, suggesting that oxandrolone treatment may have suppressed the hypothalamic-pituitary-gonadal axis." This is an admission by the investigators for induced hypogonadism. There is, in fact, a significant decrease of LH levels. LH and FSH are the regulators of testosterone production and spermatogenesis, respectively. AAS administration causes a decrease in the serum gonadotropin, LH, level that in turn results in a decrease in serum testosterone. The result of an abnormally low total testosterone in the face of an abnormally low LH is diagnostic for hypogonadotropic hypogonadism.

Changes in Luteinizing hormone (IU/L)

Treatment	Placebo	50 mg/day	100 mg/day
Baseline	5.5 ± 4.7	8.4 ± 4.4	8.7 ± 13.7
Change	1.0 ± 2.0	-6.0 ± 4.1**	-5.6 ± 9.7***

One-way ANOVA across the three groups, P=0.02; **Bonferroni-adjusted, P<0.05 for comparison to placebo (independent t-test, P<0.03); ***Bonferroni adjusted, P<0.025 for comparison to placebo (Kruskal-Wallis test, P<0.02).

STUDY 3 limitations include, "[o]xandrolone unlike testosterone is 5-alpha reduced and nonaromitizable, and blood levels for this drug are not available in clinical laboratories. This makes it difficult to determine dose–response effects or compare timing and magnitude of outcomes measured in our study to other trials using testosterone or testosterone conjugates." Oxandrolone measurements are available as seen in the study by Sheffield-Moore et al.

However, disregarding this point is that oxandrolone has a very short half-life, clinical trials are over periods of weeks, not hours or days, and serum oxandrolone measurements are of no consequence. This study limitation statement is, again, suspect.

STUDY 1 includes serum testosterone levels at baseline and week 24 (12 weeks after oxandrolone discontinuation) but no serum testosterone levels for the weeks between. The failure to measure serum testosterone because of oxandrolone cross reactivity, an assay system citing no cross reactivity with oxandrolone, use of the assay system published to be the most accurate and reliable, and use of the assay system by other investigators in the presence of oxandrolone can only raise suspicion to a very high level for other purposes, unethical and unscientific.

The studies comment the safety measures that significantly changed during treatment with oxandrolone were largely reversible. The safety measures included for this comment were cholesterol and liver function changes. No comment, even cursory, is present regarding HPTA changes. Ominous, however, is the intent and purpose of the authors by the statement, "Thus, therapy with an androgen that does not adversely affect lipids may be beneficial for some components of the metabolic syndrome in overweight older men with low testosterone levels." This statement is a proposal for the future use of testosterone in the treatment for metabolic syndrome, a syndrome known to affect thousands of individuals. These investigators dismiss and ignore the period after AAS cessation that directly influences the validity of the conclusions and threatens the potential for any future granting by the FDA for an additional indication. The potential in dollar sales for the pharmaceutical industry is in hundreds of million.

In 2003, Wittert et al. conducted a study to determine the ability of oral testosterone to prevent muscle loss in older men over a twelve-month period.[357] Sole support for the study is from Organon Pty Ltd., manufacturers of oral testosterone undecanoate (Andriol). The study was a collaborative effort that included Division of Geriatric Medicine, Saint Louis University Medical School and Geriatric Research, Education, and Clinical Center, Veterans Affairs Medical Center, St. Louis, Missouri.

The stated intention in the study was to investigate men with borderline low (eugonadal) plasma testosterone concentrations resulting from normal aging but within the overall normal male range, and to exclude those who were frankly hypogonadal. Administration of testosterone undecanoate (80 mg twice daily) was for one-year to 76 healthy men aged 60 years or older.

There was no change in body weight during the course of the study. There were no significant effects on muscle strength. Lean body mass increased and fat mass decreased in the testosterone as compared with the placebo-treated group. After 12 months, lean-body mass decreased by 0.98-kg (2.16-lb) and increased by 0.67-kg (1.47-lb) in the placebo and testosterone groups, respectively. There was no significant change in lean body mass between 6 and 12 months in either the placebo or the testosterone groups. After 12 months, fat mass increased by 0.93-kg (2.05-lb) and decreased by 0.05-kg (0.11-lb) in the placebo and testosterone groups, respectively.

The groups did not include nutrition counseling or progressive resistance training. Ignoring this proven and known effective treatment of sarcopenia, the authors' state, "The

decrease in body fat may be of significance, as it has been shown that the combination of adipose excess and muscle loss in older persons results in markedly increased morbidity." However, at 3, 6, and 12 months, luteinizing hormone (LH) was significantly lower in the testosterone group, as compared with the placebo group. This is an indication for HPTA suppression. ASIH will reverse the body composition improvements and inflict upon the patient other signs and symptoms of hypogonadism. This is the case for this study and those above. Instead of treatments that will improve the health of the elderly, these investigators treatment interventions endanger their health and welfare.

- 10 -

DOUBLETHINK: MISDIRECTION, OBFUSCATION, & CONTRADICTION

Doublethink is an integral concept in George Orwell's dystopian novel Nineteen Eighty-Four, and is the act of holding two contradictory beliefs simultaneously, fervently believing both. According to the novel, doublethink is “The power of holding two contradictory beliefs in one's mind simultaneously, and accepting both of them. . . . To tell deliberate lies while genuinely believing in them, to forget any fact that has become inconvenient, and then, when it becomes necessary again, to draw it back from oblivion for just so long as it is needed, to deny the existence of objective reality and all the while to take account of the reality which one denies—all this is indispensably necessary. Even in using the word doublethink it is necessary to exercise doublethink. For by using the word one admits that one is tampering with reality; by a fresh act of doublethink one erases this knowledge; and so on indefinitely, with the lie always one leap ahead of the truth."[358]

The concepts of doubling and "doublethink" live in contemporary human experimentation. Robert Jay Lifton describes it as "the division of the self into two functioning wholes, so that a part-self acts as an entire self." There is a long history of the double in literature, including, for example, Frankenstein (between the creator and his creature) and Dr. Jekyll and Mr. Hyde. As Dr. Jekyll explains, "This doublespeak allows us to use double standards as they suit our purposes."[359]

The previous chapter, Sarcopenia, introduces the study of an OHRP complaint, "Effects of an oral androgen on muscle and metabolism in older, community-dwelling men."[360] The complaint named the Departments of Medicine, Radiology, and Biokinesiology, Keck School of Medicine, University of Southern California, Los Angeles, California and Division of Endocrinology, Metabolism, and Molecular Medicine, Charles Drew University School of Medicine, Los Angeles, California. On June 16, 2003, a complaint was filed with the Office for Human Research Protections (OHRP), listing a series of allegations (discussed below) for violations of 45 C.F.R. 46 Protection of Human Subjects, Subpart A in a published study funded by public sources.

It is the defense of the indefensible position that hypogonadism did not occur in the research subjects of the above referenced study that points to questionable research practices, possibly crossing over to scientific or research misconduct. The one and only defense of USC/CDU against the OHRP allegations is their admission in their response that hypogonadism does not occur in the subjects, there is not an "a priori" reason to suspect hypogonadism, and their unpublished data demonstrates that no hypogonadism occurs.

The USC/CDU response demonstrates a steadfast refusal to recognize a period of hypogonadism after AAS cessation. The refusal is in the face of every peer-reviewed article investigating AAS and the HPTA published to show HPTA suppression after AAS cessation. AAS effect on HPTA physiology is in peer-reviewed literature for over fifty years. The refusal is contrary to even the basic understanding of HPTA physiology taught in the most rudimentary medical school course. It is a basic physiology principle known to even the general practitioner that HPTA homeostasis involves serum testosterone levels. It is also widely known that all AAS cause HPTA suppression.

The refusal to admit the development of hypogonadism after AAS cessation therefore results in USC/CDU admitting to no discussion or documentation of ASIH and all associated side effects (risks) from hypogonadism after AAS cessation. These include failure to provide information relating to ASIH including dose-response studies on HPTA normalization, recognition ASIH is of unknown duration and severity, thereby preventing any discussion of the full extent and seriousness of ASIH, since the aforementioned studies of HPTA normalization have not been performed it is not possible to accurately state the duration of the subject's participation, failure to document greater than minimal risk, and costs relating to ASIH treatment.

The USC/CDU responses place them in a position where there is no escape from culpability and responsibility. A critical part of any study involving AAS will include by necessity the measurement of sex hormones, which are the gonadotropins and testosterone. The federal statute, 45 C.F.R. § 46.111(a)(6), is clear the research plan make adequate provision for monitoring the data collected to ensure the safety of subjects.[361] The investigators have made no provisions. Going even further, disregarding the above what could be the possible reason for not measuring the serum testosterone within days of the last administration of oxymetholone. There is none. The investigators for the above-referenced research failed to ensure that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, as required by DHHS regulations. To not make provisions for the monitoring, measurement, of the sex hormones during the study is, in itself, a violation of 45 CFR 46.111(a)(6).

Yet, this is exactly what USC/CDU does in their response by claiming without any peer reviewed literature support, hypogonadism does NOT occur with AAS administration and continue after AAS cessation. Notwithstanding, the absurd and ridiculous nature of this argument, this stand draws USC/CDU into a position in which they attempt to defend themselves by producing data that goes against all published peer-reviewed literature.

The OHRP reviewed the University of Southern California's (USC) August 21, 2003 report and Charles R. Drew University School of Medicine and Science's (CDU) August 25,

2003 and September 27, 2004 reports, submitted in response to OHRP's July 9, 2003 and August 11, 2004 letters and made a determination regarding the referenced research. On November 5, 2004, OHRP published the determination letter, accessible at the OHRP website, regarding the complaint.[362]

OHRP maintains a list of "compliance determination" letters on their website.[363] OHRP has implemented a practice to redact from compliance oversight determination letters posted on its website any sections that discuss unresolved concerns, questions, or allegations related to an ongoing investigation. Anyone wishing to request an unredacted copy of these letters should submit a request for the unredacted letter under the Freedom of Information Act (FOIA).

On November 10, 2004, OHRP sent a letter stating, "Please do not hesitate to contact me at any time should you have any questions or wish to provide additional information." January 4, 2005, a FOIA request was sent for documents pertaining to the above referenced complaint. In June 2006, the FOIA request resulted in receipt of scattered and incomplete documents regarding the OHRP complaint. The FOIA request was resubmitted but to date no other documents have been received.

Based upon the information provided by USC and CDU, OHRP was unable to substantiate allegations one, two, three, and five. Allegations numbers four and six to fourteen concern informed consent, OHRP notes that an IRB could reasonably have made the determinations necessary for the approval of the research referenced above under HHS regulations at 45 C.F.R. § 46.111 and proper informed consent under HHS regulations at 45 C.F.R. §§ 46.116-46.117.

There is nothing in the determination letter or the response of USC and CDU that directs one to a correction or explanation for the original concerns. The few FOIA documents received raise serious questions for the protection of human research subjects. An analysis and closer scrutiny of the investigators' response shows it to be wholly without merit.

The OHRP complaint, OHRP Determination Letter, University of Southern California (USC) and Charles Drew University (CDU) responses, and FOIA documents reveal investigators that are attempting to hide, obfuscate, ignore, dismiss, fabricate, falsify, and deny facts. The statements are misrepresentations and misstatements for the actual, nondisputed facts. These also include fabrications and falsifications of published literature in order to defend the indefensible. It does not require an in-depth review to notice the contradictions outlined in the USC and CDU responses. This is inexcusable from a group of researchers assumed to be among the best in their respective fields. The details of the responses transcend reality and transport one to the Orwellian world of doublethink.

OHRP COMPLAINT LYNCHPIN – ASIH: ANABOLIC STEROID INDUCED HYPOGONADISM

The admitted lynchpin for the allegations in the initial OHRP complaint is the presence or absence of hypogonadism after AAS cessation (ASIH). This is true for the allegations regarding

the use of unsound research design, unsound research methodology, and informed consent. This is admitted by the USC/CDU response. This is inarguable.

USC/CDU response, "Our review has determined that the above-referenced research was conducted using procedures that are consistent with sound research design and did not unnecessarily expose subjects to risk of hypogonadism."[364] Likewise, the USC/CDU response for not monitoring the serum testosterone level is in the claim that "[t]here was no a priori reason to expect that the study interventions would cause hypogonadism,"[365] "[t]here was no reason to believe that hypogonadism would occur at the end of the 12-week study period, after androgen cessation,"[366] and "The study intervention [oxymetholone] that was evaluated in the referenced article did not cause hypogonadism."[367] These statements go against and are contrary to every published article on HPTA physiology, basic rudimentary endocrinology knowledge, and an effrontery to layperson and professional, alike.

Thus, whether the USC/CDU response complies with the requirements of 45 C.F.R. § 46 is an inquiry to the existence of anabolic steroid induced hypogonadism (ASIH). If ASIH does not occur, the USC/CDU response is the correct one and compliance with the regulations is not an issue. However, if ASIH occurs, even the possibility, the USC/CDU response is in error, and there is noncompliance with federal human research protection requirements.

This is the case even if there is no publication demonstrating ASIH under the identical circumstances because the available published literature in existence does show ASIH, in fact, one-hundred percent of the time. The investigators responsibility is not to ignore and dismiss data that might alter the risk/benefit results but to include such data and more importantly, protect the safety of the patient.

RESEARCH RELATED SERIOUS ADVERSE EVENTS — DEATHS

The common rule governs the composition and function of IRBs and establishes the basic rules, including informed consent, for research on human subjects.[368] FOIA documents obtained reveal a more troubling and problematic aspect of the research conducted.[369] This concern is for the serious adverse event (SAE) of death. While OHRP accepted without question or investigation the USC/CDU response, OHRP's failure in this regard includes no recognition on the deaths associated with oxymetholone administration occurring after its cessation. OHRP appears to take the stance that since the drug was discontinued there can be no association. This view is one of ignorance and if sustained makes OHRP possibly complicit, at the minimum, in the deaths of these individuals.

On February 8, 2001, a FOIA document, Adverse Event Local Medical Reviewer Form, includes a summary sheet of 34 deaths, "18 of which seem unrelated to oxymetholone use" and 16 are unknown. Included is "one event reported from USC – acute MI [myocardial infarction or heart attack] about 4 weeks after completion of treatment with oxymetholone, probably not related. No need to stop project."[370]

On June 23, 2000, a memorandum describes a post-study adverse event regarding the above referenced study.[371] The memorandum includes that on June 13, 2000, one of the principal

investigators was informed that a subject in the study had just been hospitalized with an acute MI and renal impairment. The report was "an Adverse Event occurring approximately four weeks after the study subject completed 12 weeks of study therapy on May 17, 2000."[372]

Study findings include the subject had impaired activities of daily living and used a walker for what appeared to be Parkinsonian-like movements. The subject had a comprehensive history and physical, including cardiovascular stress test, before entry into the study. During the course of the study, his muscle strength and functional performance improved and he donated his walker to a convalescent care facility. The improvement in the muscle strength and functional performance are obvious references that the subject was receiving oxymetholone during the clinical trial.

Further, the investigators state that in the context of the subject in question (original correspondence, June 23, 2000), they do not believe that participation in this study contributed to the subject's heart attack one month after completing the study. "[373] After reviewing the events of the study and results of laboratory tests done on May 18, 2000 (attached), Dr. Bhasin (Co-principal investigator for the project), and Dr. Sattler felt that it was very unlikely that the study interventions were related to the adverse events." The attached laboratory tests do not include testing for sex hormones, both luteinizing hormone and testosterone.

On August 20, 2001, a memo supplied a narrative assessment as to why the principal investigator does not think that androgen therapy increases the risk for cardiac disease.[374] The reasons enumerated discuss why during androgen therapy, androgens might increase the acute risk for a heart attack. There is no discussion or reference to the known increased risk of cardiovascular events during induced hypogonadism.

Cardiovascular disease is the major cause of death among men worldwide. Sex hormones appear to play a pivotal role in determining cardiovascular risk. Testosterone may be involved directly in the regulation of vascular tone. Evidence of an inverse correlation between testosterone levels and several cardiovascular risk factors has recently emerged.[375] This supports the view that physiological levels of androgens may protect the vasculature.

Published literature demonstrates an association between lower androgenicity and increased cardiovascular risk in men. Of importance, is if induced hypogonadism adversely affects cardiovascular risk does this translate into significant cardiovascular morbidity and mortality. In 2007, a study evaluated whether the timing of fatal myocardial infarction was influenced by the administration of GnRH induced hypogonadism.[376] The authors conclude the use of induced hypogonadism is associated with earlier onset of fatal myocardial infarctions in men age 65 years or older compared with men not treated with induced hypogonadism.

The conclusion from both hypogonadism and induced hypogonadism studies is an increase risk of cardiovascular morbidity and mortality. Investigators studying AAS use are in the expectation they are aware of the relationship between hypogonadism and cardiovascular risk factors whether those studies are definitive or not. At the very minimum, the reporting of adverse cardiovascular events during AAS administration and assuredly after AAS administration

cessation when hypogonadism is most likely would alert investigators to monitor serum testosterone levels.

Despite the reporting of an adverse cardiovascular event one month after AAS discontinuation, investigators determined, "[i]t was very unlikely that the heart attack was related to the study [AAS] intervention." There is no discussion or reference to the known increased risk of cardiovascular events during induced hypogonadism.

Despite the known increased cardiovascular risk, the investigators elect to seek not the testing of sex hormones in the subject once a heart attack occurs, make provisions for the testing of sex hormones during and after the clinical trial, and steadfastly refuse to admit that hypogonadism occurs after AAS cessation demonstrated by published literature for over fifty years. The failure to investigate minimally reasons, serum testosterone levels, for the adverse events is arrogance, unsound scientific methodology, and the use of questionable research practices.

OHRP ALLEGATIONS

Allegations include the failure to use a sound research design, sound research methodology by not making provisions for data monitoring of concern to the safety of the patients, and not giving a fully informed consent upon which to make a decision whether to participate in the clinical trial.

The research design did not take into consideration that the use of oxymetholone causes a disruption of the hypothalamic-pituitary-testicular axis (HPTA), resulting in a state of hypogonadism. The research methodology did not make provisions for data monitoring of concern to the safety of the patients, specifically for testosterone levels during oxymetholone administration and at the end of the 12-week treatment period, thus failing to monitor for a possible hypogonadal state in the subjects. Without consideration in the research design, research methodology, and data monitoring for hypogonadism during and after AAS administration, it is not possible to give a fully informed consent upon which one can make a decision to participate in the clinical trial.

Based upon the information provided by USC and CDU, OHRP was unable to substantiate allegations one, two, three, and five. Allegations numbers four and six to fourteen concern informed consent, OHRP notes that an IRB could reasonably have made the determinations necessary for the approval of the research referenced above under DHHS regulations at 45 C.F.R. § 46.111 and proper informed consent under DHHS regulations at 45 C.F.R. §§ 46.116-46.117.

OHRP accepted without question contradictory and irreconcilable statements. While these physician researchers may lapse in their attention to individual rights it is the responsibility of the OHRP to secure those rights and recognize explanations as these to be nothing more than a smokescreen to human research subject violations.

The USC/CDU response to the allegations is an exercise in Orwellian doublethink. Throughout the response is the use of doublethink present. It is difficult, if not impossible, to comprehend or understand the pervasive use of doublethink except to practice subterfuge, misdirection, and obfuscation by all means possible. Contradictory to the claim for no period of hypogonadism after AAS cessation is every published paper in print demonstrates a period of hypogonadism for unknown duration and severity after AAS cessation. There is not a single paper or study demonstrating an absence of hypogonadism after AAS cessation.

Allegation #1: The investigators failed to conduct the research using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by HHS regulations at 45 C.F.R. § 46.111(a)(1).[377]

A proven threat to the health and welfare of the individual is hypogonadism. The HPTA is an important homeostatic mechanism to maintain serum testosterone levels and reproductive capacity or spermatogenesis. A disruption in the HPTA homeostasis is, by definition, disease. The very act of AAS administration, including testosterone, induces a state of hypogonadism. At first, this concept seems confusing but quickly remedied by the definition for hypogonadism.

Hypogonadism is inadequate gonadal function, as manifested by deficiencies in spermatogenesis and/or the secretion of testosterone. The normal reference range for serum testosterone is defined by the laboratory performing the assay. Similarly, infertility definitions encompass spermatozoa density, number, and quality. Hypogonadotropic hypogonadism or secondary hypogonadism is absent or decreased gonadal function (spermatogenesis and/or the secretion of testosterone) resulting from a decrease in follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH).

A FOIA document,[378] revealed that on August 6, 2003, the meeting minutes of the Institutional Review Board of Charles R. Drew University states, "IRB members were informed by the Director of [a] letter received from Dr. Bhasin in response to allegations [on] noncompliance for this study. [Effects of an oral androgen on muscle and metabolism in older, community-dwelling men] A written response is required by Dr. Francis to OHRP by August 22, 2003."

Dr. Salehian, IRB member, led the discussion with the suggestion the investigator needs to answer questions raised by the IRB. These included defining hypogonadism as (1) sexual and secondary sexual characteristics and (2) biochemically by testosterone and luteinizing hormone levels. Further, the basis for answers to the allegation should use these definitions. A motion was made, seconded, to ask for a response from Dr. Bhasin on the questions posed by the IRB. A quorum of IRB members was present. The motion passed by a vote of 10 in favor, 0 opposed, and 0 abstentions (a total of 10 votes). Despite this recommendation by the IRB, there is no discussion, mention, or reference to the definitions of hypogonadism requested in the USC/CDU response.

The HPTA has two components, both spermatogenesis and testosterone production. They are not equivalent and, in fact, have two very separate hormonal processes for homeostasis. Nevertheless, the definitions of hypogonadism are consistent by using either reproductive

capacity, infertility, and/or biochemically by testosterone and luteinizing hormone levels. As previously stated, AAS administration induce a state of hypogonadism. This state is present during their administration but typically becomes symptomatic or manifest after AAS cessation. The confirmation of the state of hypogonadism is exhibited either by reproductive or biochemical parameters, not by symptomatology. This is critically important in the diagnostic and clinical evaluation of a patient. To do otherwise, is to ignore and dismiss the situational context of testing.

For example, countless publications study the use of testosterone as a male contraceptive agent. The simplistic reason for this is that exogenous administration will cause HPTA suppression, a decrease of sex hormones that includes endogenous testosterone production and the gonadotropins, both follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH). The absence of FSH leads to infertility, contraception, or diminished spermatogenesis. This is an induced state of hypogonadism, infertility. The absent or decreased testicular testosterone production is replaced by its external administration. The individual does not experience the adverse effects of hypogonadism secondary to decreased serum testosterone because of exogenous testosterone administration. This does not take away from the fact that the patient is in a state of induced hypogonadism for the express purpose of contraception.

The USC/CDU response notes, "[t]hat previous studies conducted by World Health Organization have demonstrated complete recovery of the hypothalamic pituitary testicular axis [HPTA] after administration of supraphysiologic doses of testosterone for a year."[379] The study tested the use of testosterone enanthate 200-mg intramuscular/week for 12 months as a male contraceptive. The primary outcome is spermatogenesis, not testosterone production. The "complete recovery" referred to in the USC/CDU response is to spermatogenesis and not serum testosterone. But even more unbelievable and astounding is the oxymoronic nature of the statement. Testosterone administration for contraceptive purposes is for the specific goal of inducing hypogonadism, infertility. Recovery implies a period of restoration or return to health from sickness. These investigators are stating there is no recovery period, none.

According to the study, recovery information is available for 85% of the men; the sperm concentration of 84% of these men has returned to 20 million/ml and 46% to their own baseline level. The median time to recovery to 20 million/ml was a range of 2.8-9.5 months. Equivalent data for return to subject's own geometric mean baseline sperm concentration are a range of 4.0-13.9 months. Thus, the data from the study affirm that the return of normal spermatogenesis may take over a year.

In the study, after starting testosterone injections, there were increases in body weight, hemoglobin, and testosterone, and decreases in testicular volume, LH, and FSH. The values returned to baseline in the recovery period. The recovery period during which there are decreases in LH and FSH are by definition hypogonadism. As stated above the recovery period lasts greater than one year. Private communications are consistent with the published literature that HPTA recovery is variable after testosterone administration.[380] However, significantly not included in the USC/CDU response is the study finding the increase in body weight reverted to normal after testosterone cessation.

In the above referenced study of the OHRP complaint, subjects received an oral androgen supplement, oxymetholone, a Class III steroid hormone with similar properties to male testosterone. The USC/CDU response asserts, "Subjects were given oxymetholone for 12 weeks at levels well below the FDA approved dosage."[381] This statement is contradicted by the manufacturer recommended daily dose in adults is 1-5 mg/kg body weight per day. The usual effective dose is 1-2 mg/kg/day. Despite this recommendation is for the FDA approved indication in the treatment of anemias caused by deficient red cell production, the oxymetholone dose administered was well within the FDA approved dosage and not well below.

The intervention, oxymetholone, belongs to the class of drugs, anabolic steroids, known to have an effect upon the hypothalamic-pituitary-testicular axis (HPTA). The disruption of the HPTA results in a state of hypogonadism in the subject that continues after oxymetholone cessation. Hypogonadism has an adverse effect upon the primary outcomes of the study. Considering the oxymetholone dosage administered in this study, there is no question that subjects were left hypogonadal post therapy. In this particular case, the intervention, oxymetholone, causes a change in the prognosis in the treatment group. This introduces bias, thus making the conclusions invalid.

Other studies cited by the USC/CDU response demonstrate hypogonadism at this oxymetholone dose.[382] The glaring absence of any mention of the effects of hypogonadism after androgen cessation is inexcusable. Of an even greater source for their heinous conduct and disregard for the public health and welfare is their own data! Safety measures in the clinical study while not including testosterone did include gonadotropins, providing and affirming the state of hypogonadism.

Indication of the HPTA suppression manifests in the hormone levels on measurement. The hormones testosterone, luteinizing hormone, and follicle-stimulating hormone are markers of HPTA functionality. AAS administration result in a decrease of serum gonadotropin levels. AAS administration, other than testosterone, likewise results in a decreased serum testosterone level. The USC/CDU response demonstrates a complete absence of AAS induced hypogonadism as well as hypogonadism itself. "The symptoms of hypogonadism . . . are associated with increases in the amount of LH in blood."[383] The serum LH level may be normal, decreased, or increased in hypogonadism. Increases in serum LH levels, hypergonadotropic hypogonadism, are indicative of primary testicular failure and ageing, not AAS induced hypogonadism.

The USC/CDU response cites, "Moreover, serum luteinizing hormone (LH) was significantly decreased . . . with the 50 and 100 mg/day [oxymetholone] doses, respectively, reflecting: a state of increased androgen hormone status"[384] and "To the contrary . . . decrease in pituitary LH levels indicates that the study subjects had increased androgen activity, as expected."[385] Both of these statements indicate a state of induce hypogonadism, exactly the observation in the male contraception study.

In typical Orwellian doublethink, the USC/CDU response includes the oxymoronic statement, "[l]uteinizing hormone (LH) concentration levels decreased in study subjects indicating that the supplement was supplying additional androgen levels and there was no hypogonadism."[386] Further, in advance of this the investigators state, "As a result, the study

subjects did not experience any hypogonadal symptoms during the term of the study." This statement's purpose is to confuse and misdirect the naïve. Anabolic steroids other than testosterone each have different properties and hypogonadal symptoms do occur during AAS administration. There is ample documentation of this in the peer-reviewed literature. Moreover, one does not even need to consult the literature since this occurs in the very subjects administered AAS in this study. FOIA documents reveal that in the middle of the study, week 6, a subject experienced elevated liver function tests and complaints of a decreased libido.[387]

The induced state of hypogonadism by increased androgen levels, masked by AAS administration, will continue after AAS cessation. The question is not whether there is a state of hypogonadism after AAS cessation, the question is the duration and severity of hypogonadism after AAS cessation. Relevant is the USC/CDU admission that, "The symptoms of hypogonadism include fatigue, loss of muscle mass, muscle strength, decreased sexual drive, and increase in body fat . . . ."[388] These are all findings that negatively influence the results of the study and the conclusions.

Further, the USC/CDU response asserts that, "The allegation that the study is not based on sound research design suggests a basic misunderstanding of the science that supports the protocol."[389] Also, "The study findings supported the researchers' hypothesis, specifically, that the administration of the androgen supplement increased muscle mass and strength and decreased fat mass in the study subjects while they received the supplement."[390] USC/CDU, disappointingly, misunderstands science and the clinical application of research findings. The Bhasin et al. study is not a template for the clinical application of AAS treatment. Far from it, the findings of the study is that testosterone, and by implication AAS, is a **modulator** of body composition. Any clinical application must take into consideration all of the physiological processes of the body and not one in complete isolation and definitely not ignoring or dismissing adverse events from a drug administration.

Unfortunately, researchers duplicated the study design above for elucidating a physiological process to using AAS treatment for many disorders. In the clinical application of AAS administration, adverse events, particularly those that directly affect the primary outcome of the study, must include their consideration. Incorrectly, the clear dose-dependent effects of testosterone on muscle size and strength and body metabolism through and beyond the physiological range was a suggestion that AAS effects may be beneficial in many medical settings.[391] This is seen in published literature with no accounting or addressing of the adverse event of HPTA suppression that occurs during AAS administration and continues thereafter.

A common thread in most investigations studying the relationship between AAS administration and physical fitness parameters[392] (body composition and muscular strength) are the findings of an increased lean body mass, increased muscular strength, and decreased adiposity. However, these are findings already made by Bhasin et al. for the elucidation of the role of testosterone in muscle growth, muscle strength, and body fat. The investigations using AAS administration in various clinical disorders have not added to the literature in their treatment and more than likely have subjected countless patients to harm and even death.

While androgens have proven effective to increase lean body mass and strength under clinical trials, only after careful scrutiny and under specific conditions can translation of these findings to clinical practice take place. The consistent fact amongst these studies is that AAS administration induces a state of hypogonadism that takes a variable amount of time after AAS cessation to return to normal. The follow-up of clinical investigations using AAS administration rather than tell the improvement in body composition changes is a history of the tolerance of certain diseases to the stress of hypogonadism after AAS cessation. A period in which the patient not only loses the gains or benefits from AAS administration but also placed in a disease state worse off than when first administered AAS.

These medicines are not without their inherent problems. Anabolic steroid induced hypogonadism is a fact of AAS administration. Once there is removal of external testosterone administration, HPTA homeostasis will attempt to return. This includes hypothalamic production of releasing factor GnRH, pituitary production of FSH and LH, and testicular production of testosterone and spermatozoa. It is common knowledge that upon AAS cessation, HPTA homeostasis does not immediately return. There is not a single study within the peer-reviewed literature demonstrating an immediate return of HPTA homeostasis upon AAS cessation. In fact, for the most part this is an unstudied area of AAS, the known facts are HPTA suppression occurs after AAS administration, and the return of HPTA homeostasis is of an unknown duration and severity. This is a physiological fact for all known AAS.

Allegation #2: The investigators for the above-referenced research failed to ensure that the risks to the subjects are reasonable in relation to the anticipated benefits, as required by HHS regulations at 45 CFR 46.111(a)(2).[393]

Allegation two of the OHRP complaint is the risks are clearly beyond minimal and more importantly are incalculable. Since there are no dose-response studies relating oxymetholone and HPTA normalization, it is not possible to determine accurately the extent of hypogonadism that each subject will suffer after androgen cessation. Admission, of as much, is within the USC/CDU response. No studies exist which describe the normalization of the HPTA and the extent of hypogonadism in subjects after androgen withdrawal. As a result, the risks to the subjects were not reasonable in relation to the anticipated benefits.

The investigators are unable to stop from putting their foot in their mouth, repeatedly. The doublethink and doublespeak is obvious in their closing paragraphs in rebuttal to allegation two. The investigators state, "[t]he allegations raise an interesting research question from a scientific point of view since we are not aware that the recovery period after androgen cessation has ever been specifically studied."[394] This statement, alone, is enough to demonstrate the investigation is utilizing an unsound research design. This would have been sufficient, but they found it necessary to qualify their statement, "However, the results of such research, if it ever were determined to be sufficiently significant for clinical study, would not have impacted the design of this study nor the informed consent process for study subjects."[395]

In the first statement, the recovery period after androgen cessation is an interesting research question. However, in the second statement the question of recovery after androgen cessation is not been determined to be sufficiently significant for clinical study. These responses

are perfect Orwellian doublethink. This research is an interesting subject for investigation but we will not investigate the question to see if it is sufficiently worthy of investigation. Therefore, it is a subject not interesting enough for investigation. And, if we had investigated the subject, which we did not, there is no information to be gained from such an investigation that would change the results of our initial investigation. Because even though the subject was never investigated we already know that the results, adverse or not, are of no matter, weight, or bearing on our decisions. Therefore, hypothetically, if the drug treatment did cause cancer, this might be an interesting subject for further inquiry but since we are not researching cancer and this occurs after the drug treatment discontinuation, it has no relevance to our drug treatment investigation.

Does this scare you as much as it does me? The following statement from the USC IRB chair surpasses the level of arrogance above. "[n]or were investigators required to investigate if hypogonadism occurred."[396] The IRB responsibility is to protect the human research subject from undue risk. Here, the IRB chairperson unequivocally states that if a known harm, hypogonadism, occurs with the drug treatment there is no responsibility on the part of the investigators to inquire further either to potential patient harm or to an adverse effect upon the data and the conclusions drawn thereof. This statement, alone, is sufficient to demonstrate a violation, in principle, of federal statute 45 C.F.R. 46 Protection of Human Subjects.

The defense of the indefensible goes further. In an attempt to circle the wagons and fend off any semblance of criticism, the chairperson states, "Nor are we aware of any researchers who were required to follow subjects after treatment cessation."[397] Just in case, none of the doublethink and doublespeak has thus far persuaded you, we are only doing what everyone else does, therefore we are correct. We are right since there are others doing the same thing. This claim is possibly the most frightening in the admission of others following the very same research methodology. Following their line of reasoning if they are not right, than the use of unsound scientific methodology is rampant in the anabolic steroid published literature. This is the case.

OHRP determination letter and FOIA documents note the following points outlined in the USC and CDU responses. The investigators and the HSC IRB complied with federal regulations by ensuring that risks of hypogonadism to subjects after androgen cessation were reasonable in relation to anticipated benefits. The investigators detail that no similar studies previously conducted reported any evidence of hypogonadism after androgen cessation. It is important to remember that a number of prior studies have been conducted involving the administration of androgen supplements in males.

Previously discussed is the published literature demonstrating hypogonadism after AAS cessation. The chapter is but a brief collection of the peer-reviewed literature definitively showing the presence of anabolic steroid induced hypogonadism. In fact, in a clear act of misdirection the investigators never cite a single study that hypogonadism does **NOT** occur after AAS cessation. This is because there is none. It is a maxim that after AAS administration, HPTA suppression follows, with the variables being the duration and severity.

The assertion that “no similar studies reported evidence of hypogonadism after androgen cessation,”[398] is groundless and false. One must assume that the researchers have access and

knowledge to use Medline. The effects of androgenic-anabolic steroids on the hypothalamic-pituitary axis have been known for over fifty years. This is true for licit and illicit androgenic-anabolic steroids.

In a bold and outright lie, the response states, "There is no evidence from any prior research to suggest that androgen cessation resulted in a risk of hypogonadism."[399] Further clarification of the statement is within the footnote, "Previous studies that used oxandrolone, a synthetic androgen with similar anabolic activity, reported no change in serum testosterone levels during oxandrolone administration (Sheffield-Moore et al, 1999)."[400] According, to the investigators the study reports the use of oxandrolone, a synthetic androgen with similar anabolic activity, found no change in serum testosterone levels during oxandrolone administration.[401] The very study cited by USC did report a change, a significant decrease, in serum testosterone. Administration of oxandrolone was for only 5 days in the study by Sheffield-Moore et al. In a complete contradiction to the USC claim, the study found serum total and serum free testosterone concentrations by day 5 significantly reduced below day 0 and day 3 values. The study results demonstrate significant decreases in both LH and testosterone. This is a direct contradiction and a lie.

Other literature cited by the USC IRB chairperson includes a number of publications that do contain results for the sex hormones during AAS administration.[402] Regarding use of the very same AAS, oxymetholone, in the OHRP study complaint, the USC/CDU response cites publications by Hengge et al.[403] Determinations of serum total testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) every 4 weeks during the 16-week studies were found to decrease markedly and significantly upon the intake of oxymetholone. LH and FSH are the regulators of testosterone production and gonadal function. The result of an abnormally low total testosterone in the face of an abnormally low LH is diagnostic for hypogonadotropic hypogonadism. The etiology is clear, anabolic steroid induced hypogonadism. By all available published literature, including citations by the investigators, AAS administration induce a state of hypogonadism after their cessation.

The investigators, though, continue with the Orwellian logic of doublethink and claim that even if hypogonadism occurs after AAS cessation, it is of a duration and severity so brief to not matter.[404] Again, this is with no evidence to support their claim because the claim is not sufficiently interesting to warrant investigation. In other words, there is no reason to investigate the unknown since the unknown is not important and even if the unknown is important it only exists for an unknown duration and severity. Therefore, the unknown is not relevant. Orwellian doublethink perfected.

The investigators argue in the USC/CDU response that the investigators who conducted the above referenced study also performed a subsequent study, which demonstrated that testosterone levels did return to normal function quickly. This study, "Treatment with Oxandrolone and the Durability of Effects in Older Men," is discussed previously.[405] The investigators conducted a follow-up study using oxandrolone (oral androgen similar to oxymetholone) at the licensed dose for weight loss (20-mg/day) for 12 weeks in older men. The purpose of the second study was to assess the durability of effects of treatment on measures of skeletal muscle strength and body composition 12 weeks after discontinuing oxandrolone (study

week 24). The table below shows that testosterone levels at baseline and 12 weeks after oxandrolone treatment discontinuation (study week 24).

Testosterone ng/dL	Baseline	Week 24	P values
Oxandrolone (n=20)	369±147 ng/dL	358±119 ng/dL	0.28
Placebo (n=12)	357±153 ng/dL	421±196 ng/dL	0.26
P values	0.83	???	

The investigators conclude in their response, "These data confirm that oxandrolone treatment discontinuation did not produce hypogonadism."[406] The data in the table does not include the *P*-values for comparison between oxandrolone and placebo at week 24, which are critical to understand the results of the study. Notwithstanding, the data presented in the table differs from that in the published study, the data does not confirm that oxandrolone treatment discontinuation did not produce hypogonadism.

The table shows the results for the baseline and week 24 only, but not for week 1-12 during oxandrolone administration and most importantly week 13-23 after oxandrolone discontinuation. Not surprisingly, absent from the USC/CDU response is the result of the oxandrolone study. The study found that the positive changes in lean body mass, muscle area, and strength produced by oxandrolone in the study had completely disappeared twelve weeks after AAS cessation. This was undoubtedly due to the state of hypogonadism induced by the administration of oxandrolone, anabolic steroid induced hypogonadism (ASIH). Rather than prove "oxandrolone treatment discontinuation did not produce hypogonadism" the study proves that an effect, hypogonadism, does occur after AAS cessation that completely negates the positive effects of lean body mass, muscle area, and strength from oxandrolone administration. These results are conveniently missing from the USC/CDU response. The conclusion by the investigators is another showing of utter arrogance, disdain, and contempt to those who question their scientific methodology.

Perhaps the most absurd and far-fetched reasoning for a rational behind their failures for an informed consent and to account for the effects of hypogonadism after androgen cessation on body composition is the “risk of hypogonadism is not listed as part of the Food and Drug Administration-approved labeling of oxymetholone,” and "even the Physicians' Desk Reference (PDR) does not list hypogonadism as a possible risk of androgen cessation after treatment with oxymetholone."[407] In other words, the Food and Drug Administration (FDA) approved labeling of oxymetholone does not include the risk of hypogonadism.

The OHRP should take these investigators to task for an indefensible position. Are these investigators stating unequivocally that the extent of their knowledge is limited to the “FDA approved labeling” or more commonly known as the PDR? However, have these investigators forgotten that their research is **NOT** studying the FDA approved use of oxymetholone? Below are excerpts from the 2000 PDR that have not changed and are identical to those of the 2004 PDR.

FDA APPROVED LABELING OF OXYMETHOLONE: CLINICAL PHARMACOLOGY

"Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. . . . They suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes."

Carcinogenesis, Mutagenesis, Impairment of Fertility: "However, as noted below under ADVERSE REACTIONS, oligospermia in males and amenorrhea in females are potential adverse effects of treatment with ANADROL® Tablets. Therefore, impairment of fertility is a possible outcome of treatment with ANADROL® Tablets."

ADVERSE REACTIONS

In Men: "Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence . . . ."

The investigators expect by offering an approved document of a U.S. agency irrefutable and unrebbuttable support for their position. Did the investigators believe the OHRP would not read the "approved labeling of oxymetholone"? Apparently, the OHRP clearly did not bother to check to see if what the investigators stated to be true was in fact true. The PDR unequivocally states that hypogonadism is a result of oxymetholone administration.

Allegation #3: The investigators for the above-referenced research failed to ensure that the selection of subjects is equitable, as required by HHS regulations at 45 C.F.R. § 46.111(a)(3).[408]

OHRP notes the following points outlined in the USC and CDU responses that previous studies have shown that testosterone administration to healthy young men resulted in increased muscle size and strength. However, previous studies on the effects of testosterone administration in older men were inconsistent. Since the subjects in the above-referenced research were community-dwelling men at risk of sarcopenia and frailty, they were an appropriate population for the study.

Aside from the regulatory requirement that IRBs provide additional protections for specified vulnerable persons, there are no specific regulations governing research with elderly subjects. A growing number of clinical trials are being conducted on treatments for illnesses that affect senior Americans. Older generations of Americans have typically held a more trusting view of health professionals. As a result, this population may be more vulnerable to being influenced to participate in clinical trials.

The research failed to consider the possible adverse outcome of hypogonadism in the study design, and utilized a study population that may be more vulnerable to this condition. The investigators determined stand that there is no risk of hypogonadism after AAS cessation is their lynchpin the choice of the elderly is safe. However, this argument fails horribly in their admission that the period after AAS cessation is not a studied area thereby refuting their own argument on hypogonadism after AAS cessation. More heinous is the investigators feigned ignorance for basic HPTA physiology and that all published literature demonstrates AAS

induced HPTA suppression. There is not a single publication showing an absence of HPTA suppression with AAS administration.

The USC/CDU response did not address the unstudied area of hypogonadism after AAS cessation. Instead, the response simply states that, "The issue of whether androgen administration improves muscle strength has important implications; if androgen administration does not improve muscle performance, then there is little clinical utility in administering androgens to older men or men with chronic illness." This is an even stronger reason to consider the period after AAS cessation, by their statement. In fact, published literature by these same authors demonstrate no significant change in muscle mass or strength 12 weeks after AAS cessation that is preceded by 12 weeks of AAS, oxandrolone, administration.

Prior to performing clinical research on vulnerable populations, it would be imperative to establish clearly the clinical safety of the androgen. The research study failed to consider and account for the adverse outcome of hypogonadism after oxymetholone cessation. Before investigations were conducted on a vulnerable population, elderly, the period of androgen induced hypogonadism should be studied and published in healthy young men. The safety studies, once performed, should be done in a population that is not vulnerable to increased health risks (e.g., elderly).

Nonetheless, even if one were to assume for argument purposes the validity of the research in an elderly population, the investigators fail to explain a population of men at risk for sarcopenia and frailty. The doublethink response, again, confuses the primary outcome of the study by use of interjecting the terms sarcopenia and frailty. In order to identify individuals at risk for sarcopenia and frailty, there must be criteria. But more ridiculous is that sarcopenia occurs in all aging persons. The investigators misuse the term sarcopenia as a condition for which community-dwelling men are at risk. “Sarcopenia is the loss of muscle mass and strength that occurs with aging. It is a consequence of normal aging, and does not require a disease to occur.”[409] Thus, the use of the term sarcopenia is nonsensical and valueless.

Frailty is a complex syndrome and still lacks a standard definition.[410] “Frailty is a state of reduced physiologic reserve associated with increased susceptibility to disability.”[411] Recent literature has defined frailty as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.[412] Current research is directed towards identifying biological markers that may characterize the frailty syndrome.[413] Thus, there are no standard criteria for identifying those at risk for frailty. The authors did not include any criteria for frailty. Therefore, the use of this marker is also nonsensical and valueless.

Allegation #5: The investigators for the above-referenced research failed to ensure that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, as required by HHS regulations at 45 C.F.R. § 46.111(a)(6).[414]

Allegation five of the OHRP complaint is the investigators' failure to assay and measure the serum testosterone level. This is potentially the most serious and flagrant disregard for the protection of human subjects. As detailed in prior chapters, AAS effect on HPTA physiology is

in peer-reviewed literature for over fifty years. It is a basic physiology principle known to even the general practitioner that HPTA homeostasis involves serum testosterone levels. It is also widely known that all AAS cause HPTA suppression. A critical part of any study involving AAS will include by necessity the measurement of sex hormones, which are the gonadotropins and testosterone. To not make provisions for the monitoring, measurement, of the sex hormones during the study is, in itself, a violation of 45 CFR 46.111(a)(6).

Adequate is sufficient to satisfy a requirement or meet a need. Provision is the activity of supplying or providing something, arrangement or preparation beforehand. Definitions of providing include (1) to make available; furnish, (2) to take measures with due foresight, and (3) to arrange for or stipulate beforehand, as by a provision or proviso. It is inarguable the federal statute is clear, monitoring of data to ensure patient safety is to be available. An interpretation the statute provides that data monitoring be not available is doublethink taken to an extreme. Yet, this is the interpretation by USC/CDU and readily accepted by OHRP without question or argument.

The investigators include within the METHODS section for Safety Monitoring, "We did not test for total and free testosterone levels at the end of the 12-wk treatment period, because semisynthetic androgens including oxymetholone cross-react in these assays for testosterone." There is an absence of any citations in support of their problem of cross reactivity of semisynthetic androgens in RIA of serum testosterone. This statement is nothing more than a cover-up for the questionable research practices and unsound scientific methodology of the investigators. This is evident by the doublethink reasons offered by the investigators.

Of note is that only in publications by these investigators is there a claim made for an inability to measure serum testosterone in the presence of semisynthetic androgens. Other than the above reference study with oxymetholone and the studies on oxandrolone is this claim of cross reactivity found. The explanation that cross reactivity with semisynthetic androgens lead to the inability to measure serum testosterone is not present in any other peer-reviewed publication with an AAS in a clinical study. This fact along with the obligation of the investigators provided by 45 CFR 46.111(a)(6) is troublesome and problematic.

Several laboratory assays and methods of calculation are used to measure testosterone: total testosterone (T = protein bound + free), free testosterone (FT = not bound to proteins), and bioavailable testosterone (BT = free + albumin bound). The methods used to conduct the measurements vary in their accuracy, standardization, the extent of validation, and the reproducibility of results. Radioimmunoassay measurement of total testosterone is a validated, standardized, and reproducible assay.[415] As background, the following is a discussion of radioimmunoassay terms and principles.

In radioimmunoassay (RIA), a fixed concentration of labeled tracer antigen, testosterone, is incubated with a constant amount of antiserum such that the concentration of antigen binding sites on the antibody is limiting, for example, only 50% of the total tracer concentration may be bound by antibody.[416] If unlabeled antigen, serum testosterone, is added to this system, there is competition between labeled tracer and unlabeled antigen for the limited and constant number of binding sites on the antibody, and thus the amount of tracer bound to antibody will decrease as

the concentration of unlabeled antigen increases. This can be measured after separating antibody-bound from free tracer and counting the bound fraction, the free fraction, or both. A calibration or standard curve is set up with increasing amounts of known antigen, and from this curve, the amount of antigen in the unknown samples can be calculated. Thus, the four components for a radioimmunoassay system are an antiserum to the compound to be measured, the availability of a radioactively labeled form of the compound, a method whereby antibody-bound tracer can be separated from unbound tracer, and a standard unlabeled material.

Specificity is one of the most important requirements of immunoassays. Interference occurs in all situations in which the antibody is not specific for the analyte. Consequently, assessment of specificity is a vital step in the optimization of every new immunoassay. Poor specificity results in interference from compounds of similar molecular structure or which carry similar immunoreactive epitopes. An epitope is a localized region on the surface of an antigen that is capable of eliciting an immune response and of combining with a specific antibody to counter that response.

Estimation of antibody cross-reactivity was originally determined by incubation of a fixed antibody concentration with varying concentrations of analyte (A) and cross-reactant (C) in the presence of a fixed concentration of labeled analyte (A*) and determined from the formula: Percentage cross-reactivity = (Mass of analyte A required to displace 50% of A*/Mass of cross-reactant C required to displace 50% of A*) X 100.

In determining the overall specificity of an assay, a major factor is the cross-reactivity of the antibody. The extent to which cross-reacting substances affect an assay depends on a number of factors: their concentration relative to the analyte, their relative antibody-binding affinities, and the assay design. However, other steps such as preanalytical purification (e.g. extraction and/or chromatography) can be used to eliminate unwanted interference and improve assay specificity.

Cross-reaction is the binding or interference in the binding of the antibody by some agent other than the compound chosen to be measured. Specification sheets accompanying antibody shipments usually supply known cross reactivity information in table form for other materials typically present in the measured sample material that may cross-react with the antibody.

According to the investigators, RIA using iodinated testosterone as tracer (no. 07-189102; ICN Biomedical, Costa Mesa, CA), measured total testosterone concentrations. However, the investigators propose and proffer their failure to do so is by the nature of the complexity of the sex hormone measurement for testosterone. In 1998, these same investigators, F. Sattler and S. Bhasin, published the use of sensitive assays for the measurement of total and free testosterone levels.[417] The testosterone concentrations in the dialysate were measured by an iodinated RIA, using ^{125}I-labeled testosterone purchased from ICN Pharmaceutical Co. (Irvine, CA). This is the same RIA kit used in the above referenced study. Technical documentation provided with the RIA kit, ICN Biomedical no. 07-189102, provides the following cross reactivity table:

Compound	% Cross Reaction

Testosterone	100
5α-Dihydrotestosterone	3.40
5α-Androstane-3β, 17β-diol	2.20
11-Oxotestosterone	2.00
6β-Hydroxytestosterone	0.95
5β-Androstane-3β, 17β-diol	0.71
5β-Dihydrotestosterone	0.63
Androstenedione	0.56
Epiandrosterone	0.20
11β-Hydroxyandrostenedione	<0.01

All other steroid compounds tested at a cross reactivity of <0.01%, including oxymetholone. A personal inquiry to technical support of ICN Biomedical, Costa Mesa, CA did not support the statement that oxymetholone is a significant problem of cross reactivity with the RIA kit for serum testosterone. Additionally, there are techniques available to determine cross-reactivity, which are neither difficult nor unwieldy.

The USC/CDU response to the manufacturer specifications of the RIA kit, RIA methodology, and more is another exercise in Orwellian doublethink. The USC/CDU response admits they verified that the cross reactivity of oxymetholone was indeed relatively small, in the area of 1-2%.[418] Although this cross reactivity is far greater than that specified by the RIA kit, the USC/CDU response states this small cross reactivity ignores other issues and "reflects naiveté about radioimmunoassays."[419]

These issues according to USC/CDU include they "did not know (and still do not know) what the circulating concentrations of oxymetholone are after administration of 50 and 100 mg of this drug."[420] USC/CDU propose that "[i]f the circulating concentrations of oxymetholone are in 10,000-ng/dL range, as we suspect they might be, they could contribute very substantially to the measured testosterone immunoreactivity."[421] They propose that they know the cross reactivity is small, 1-2% by their methodology (far greater than the less than .01% by the manufacturer), but without knowledge of the serum oxymetholone concentration this is of no assistance. Since 1-2% of 10,000-ng/dL (by their guess for a possible serum oxymetholone concentration) is equal to 100-200-ng/dL, this is a prohibitive amount for an accurate serum testosterone measurement.

Oxymetholone published pharmacokinetics demonstrates the argument for serum oxymetholone concentrations and cross reactivity is groundless. The pharmacokinetic parameters in healthy volunteers of the oral administration of 50-mg oxymetholone are C(max) and T(max) of 18.8-ng/ml and 3.5-hours (2.75-4.00), respectively; 10 hours posttreatment level 4.0-ng/ml; elimination half-life of 8.0 hours; and Vd 2.7-L.[422]

The issue of cross reactivity even at the much greater 1-2% level cited by the USC/CDU response would not be a factor in the serum testosterone measurement. The USC/CDU response

states the reason these serum testosterone levels are not included in the publication is "[b]ecause the investigators could not resolve the issue of cross reactivity with any degree of certainty and therefore could not assure the accuracy of the testosterone measurements, they did not report the data on testosterone levels in the above manuscript."

Using the C(max) attained after a 50-mg oxymetholone dose of 18.8-ng/ml, or 1880-ng/dL, and the much larger cross reactivity of 1-2% of the CDU laboratory, rather than the less than 0.01% specifications, the maximum cross reactivity is 37.6-ng/dL (at 0.01%, the maximum cross reactivity is less than 1-ng/dL). This occurs only if the blood sample is obtained within 3.5 hours of oxymetholone administration. If the sample is taken 10 hours after oxymetholone administration, i.e., in the morning after the prior evening administration, the oxymetholone concentration is 4.0-ng/mL, or 400-ng/dL. In this circumstance, the maximum cross reactivity, using the much larger cross reactivity of 1-2% of the CDU laboratory, is 8-ng/dL.

Thus, according to these investigators they have no control on the dosing schedule and no control on the blood sampling, therefore, no control on oxymetholone concentrations. How absurd and ridiculous are these claims. Nevertheless, the federal statutes, 45 C.F.R. § 46.111(a)(6), is clear the research plan makes adequate **provision** for monitoring the data collected to ensure the safety of subjects. The investigators have made no provisions. There is obviously no plan, a violation of the statute. Going even further, disregarding the above what could be the possible reason for not measuring the serum testosterone within days of the last administration of oxymetholone. There is none.

However, the study methodology includes "Adherence was monitored by pill counting at each study visit." Thus, the investigators had control over the administration and dosing schedule. The investigators for obvious reasons have complete control on blood sampling. A claim by the investigators that oxymetholone, or its metabolites, interference (cross reactivity) with the testosterone assay precluded an accurate determination is highly suspect.

Moreover, the oxymetholone pharmacokinetics demonstrates that the serum level of 10,000-ng/dL does not occur with 50-mg or 100-mg oxymetholone administration. However, if one accepts the serum concentration from the USC/CDU response, the oxymetholone dose administered to arrive at this oxymetholone concentration can be calculated.

The volume of distribution (Vd), also known as apparent volume of distribution, is a pharmacological term used to quantify the distribution of a medication throughout the body after oral or parenteral dosing. Volume of distribution is the volume the amount of drug would need to be uniformly distributed in to produce the observed blood concentration.

The volume of distribution is given by the following equation: Vd = Total amount of drug in body/Plasma drug concentration. Therefore the dose required to give a certain plasma concentration can be determined if the Vd for that drug is known. The Vd is not a real volume; it is more a reflection of how a drug will distribute throughout the body depending on several physicochemical properties, e.g. solubility, charge, size, etc. This concept is important to understand the absurdity of the investigators claim regarding cross reactivity.

The formula above can be used in a number of ways. For a known Vd, one can calculate the approximate dose administered for a known steady-state plasma drug concentration. Alternatively, for a known Vd, one can calculate the approximate steady-state plasma drug concentration for a known amount of drug administered.

In this case, one can use the formula Vd = (Total amount of drug in body/Plasma drug concentration), where Vd = 2.7-L or 27-dL, to calculate the dose administered. To arrive at a serum testosterone concentration 10,000 ng/dL, the individual would need to administer 270-mg oxymetholone (10,000 ng/dL x 27 dL = 270,000 ng = 270 mg), more than 2.5 times the known administration.

USC/CDU states that since that do not have an assay for the measurement of serum oxymetholone concentrations, it was therefore not possible to determine the exact contribution of oxymetholone cross reactivity to the measured testosterone concentrations. Additionally, USC/CDU said, "A more difficult issue that we faced was that the metabolism of oxymetholone in humans had not been studied in detail, and we did not know whether and how much the various metabolites of oxymetholone cross-react in testosterone assay or whether these metabolites are biologically active."[423]

These explanations offered by USC/CDU do not bear up upon scrutiny and expose the use of doublethink, again. Oxymetholone, as well as oxandrolone, metabolism has been studied extensively in humans.[424] This includes their metabolism. The classical paper, in 1996, is by Schanzer that presents an excellent overview and discussion of AAS metabolism and activity of the metabolites.[425]

The far-fetched and ridiculous nature of their claims is evident in that even the layperson knows that the detection of AAS and their metabolites have been an integral and instrumental part of testing in athletes. Athletes to improve their physical performance misuse anabolic androgenic steroids (AAS) to a high extent in sports. Sports federations consider the use of these drugs in sports as doping. The misuse of AAS is controlled by detection of the parent AAS and their metabolites.

Notwithstanding, there are peer-reviewed publications containing measurements of testosterone in the presence of oxymetholone administration. Literature cited by the USC IRB chairperson includes a number of publications that do contain results for the sex hormones during AAS administration.

Regarding use of the very same AAS, oxymetholone, in the OHRP study complaint, the USC/CDU response cites publications by Hengge et al.[426] Determinations of serum total testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) every 4 weeks during the 16-week studies were found to decrease markedly and significantly upon the daily intake of 100-mg oxymetholone. The serum testosterone and luteinizing hormone (LH) values for the baseline and week 16 with oxymetholone 100-mg/day are shown in the table below.

Oxymetholone 100-mg/day

	Baseline	Week 16	Change	P-Value
Testosterone (ng/dL)	590 + 260	170 + 90	-420 + 60	P<.0001
LH	4.9 + 3.4	1.7 + 1.8	-3.2 + 0.7	P<.0005

LH and FSH are the regulators of testosterone production and spermatogenesis, respectively. AAS administration causes a decrease in the serum gonadotropin, LH, level that in turn is reflected in a decrease in serum testosterone. The result of an abnormally low total testosterone in the face of an abnormally low LH is diagnostic for hypogonadotropic hypogonadism. The etiology is clear, anabolic steroid induced hypogonadism. The investigators include in their study published change in safety measures for LH after 12 weeks of study therapy (Table 2).

Luteinizing hormone (U/L)

Treatment	Placebo	50 mg/day	100 mg/day
Baseline	5.5 ± 4.7	8.4 ± 4.4	8.7 ± 13.7
Change	1.0 ± 2.0	-6.0 ± 4.1**	-5.6 ± 9.7***

One-way ANOVA across the 3 groups, P=0.02; **Bonferroni-adjusted, P<0.05 for comparison to placebo (independent t-test, P<0.03); ***Bonferroni adjusted, P<0.025 for comparison to placebo (Kruskal-Wallis test, P<0.02).

In Orwellian doublethink, the USC/CDU response proposes since "[s]erum LH concentrations were suppressed modestly; this led us to suspect that either oxymetholone or one of its metabolites was cross reacting in testosterone assay." More than "suppressed modestly," the LH level is significantly decreased. Elsewhere, the USC/CDU response admits, "Moreover, serum luteinizing hormone (LH) was significantly decreased . . . with the 50 and 100 mg/day doses, respectively, reflecting: a state of increased androgen hormone status."

These statements are a clear example of misdirection and obfuscation. The admission, and publication, by USC/CDU of a significantly decreased LH level does demonstrate "a state of increased androgen hormone status." The significantly decreased LH level poses a very serious problem for the USC/CDU investigators. The possible USC/CDU explanations:

(1) The decrease in LH level necessarily results in a decrease in serum testosterone level. Despite this explanation to be the correct one by the uniformly and unanimous findings in published literature, this explanation is excluded by the USC/CDU response that steadfastly and stubbornly states there is no hypogonadism, during AAS administration or after AAS cessation. An admission of hypogonadism places USC/CDU in violation of 45 C.F.R. § 46, the original OHRP complaint. Thus, there adamant denial of hypogonadism leaves only two other alternative explanations.

(2) The decrease in LH level necessarily results in a decrease in serum testosterone level, but cross reactivity of oxymetholone in the testosterone assay masks the decrease. Reduced LH levels as evidence of cross reactivity since the reduced LH levels translate into decreased serum

testosterone. Since there are no decreased serum testosterone levels, cross reactivity must be an issue. This is an admission by USC/CDU for decreased serum testosterone or hypogonadism.

USC/CDU recognizes this and offers the explanation that the cross reactivity of oxymetholone in the testosterone assay. This would include admitting to decreased serum testosterone levels. However, in offering this explanation USC/CDU admits to a state of hypogonadism, placing it in violation of 45 C.F.R. § 46. At the very least, the violation is for not making adequate provisions for the safety monitoring of the subjects. Acknowledging this potential culpability and responsibility, USC/CDU, instead, presents data that oxymetholone administration does not result in a decrease serum testosterone (shown and discussed below).

(3) The decrease in LH level does not result in a decrease in serum testosterone level. Despite the published literature, USC/CDU response takes this position. USC/CDU has by their own arguments place themselves in no other position than to deny the effects of a decreased LH upon serum testosterone. This is an untenable position. As such, the data presented by USC/CDU in defense of this position, if from the study subjects, is evidence of research misconduct.

Reduced LH levels as evidence of an increased androgen state and USC/CDU proffers that the serum testosterone level did not significantly change. USC/CDU is unable to use the cross reactivity issue since cross reactivity would result in the serum testosterone level to increase. The serum testosterone level would reflect the unchanged serum testosterone plus the cross reactivity of oxymetholone resulting in an increase of serum testosterone.

USC/CDU response is for an oxymetholone effect to reduce LH serum concentration, a reduced LH not to translate into a decreased serum testosterone, an oxymetholone effect to cause an increased androgen state, and a conclusion of no HPTA effect of oxymetholone is vintage Orwellian doublethink. This position is untenable. In an apparent desperate attempt to substantiate this position, USC/CDU offers serum testosterone measurements in subjects receiving 100-mg/day oxymetholone.

By all available peer-reviewed published literature, none of the responses offered by USC/CDU explains or clarifies their inability to measure serum testosterone. But, in typical Orwellian fashion, the USC/CDU response states that they did measure serum testosterone. In contradictory and irreconcilable statements, the investigators provide the identical table for serum testosterone measurements in both **three** and **four** men treated with 100-mg/day oxymetholone at baseline and after six and twelve weeks of treatment. Further, the levels found by USC/CDU did not show a significant change from baseline. Despite the obvious difference in the reporting of three and four men, neither USC nor CDU made a correction and OHRP did not question the discrepancy.

Total Testosterone (ng/dL)

Oxymetholone 100-mg	Baseline	Week 6	Week 12
Mean±SEM	457±65	370±40	370±131

This data is seriously problematic. If the data presented are not from subjects of the study, than there should be evidence for an investigational study. It is unfathomable, though believable; this would occur without IRB approval and informed consent. The wording of the response does not make this clear and the only manner to decide this issue is by an investigation into this by the institution, itself, or by the Office of Research Integrity (ORI).

A good faith[427] complaint was submitted for scientific misconduct as provided by 42 C.F.R. Part 50, Subpart A Responsibility of PHS Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science.[428] The complaint, specifically, is misconduct in the recording and reporting of serum testosterone measurements in the above referenced study.

Scientific misconduct means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. Consistent with the Office of Science and Technology Policy (OSTP) government wide definition and guidelines on research misconduct, the new rule uses the term "research misconduct" rather than "misconduct" or "misconduct in science." Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. (a) Fabrication is making up data or results and recording or reporting them. (b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

Without investigating this possibility, the ORI summarily dismissed a complaint of possible research misconduct.[429] Apparently, the ORI by some methodology is able to determine these are not the same subjects. If as stated above the data presented by USC/CDU in defense of this position, if from the study subjects, is evidence of research misconduct.

The serum testosterone values provided by FOIA documents demonstrate by a mathematical certainty falsification for inclusion of subjects in the study or the serum testosterone measurements. Baseline serum testosterone measurements for the three groups provided in the study are the following. The number of subjects in each group is within parentheses. The values are the Mean ± SEM.

Baseline Total testosterone (ng/dL)

Placebo (11)	Oxymetholone 50 mg/day (11)	Oxymetholone 100 mg/day (9)
382 ± 86	382 ± 79	360 ± 141

The FOIA documents provide data that allows a comparison for the treatment 100-mg oxymetholone. The baseline data states for this treatment group there are 9 subjects with a serum total testosterone (Mean ± SEM) of 360 ± 141 ng/dL. The FOIA data provided for this group is for either 3 or 4 subjects at baseline, week 6, and week 12.

Testosterone (ng/dL)

Oxymetholone 100-mg/day	Baseline	Week 6	Week 12
Baseline (9)	360 ± 141	-	-
USC/CDU (3 or 4)	457±65	370±40	370±131

From this data, one can calculate the baseline mean of the remaining 6 or 5 subjects. If the FOIA data represents 3 values, the remaining 6 values will have a mean equal to 312.[430] If the FOIA data represents 4 values, the remaining 5 values will have a mean equal to 282.[431]

The difference between the means of two samples, A and B, both randomly drawn from the same normally distributed source population, belongs to a normally distributed sampling distribution whose overall mean is equal to zero and whose standard deviation ("standard error") is equal to $\sqrt{[(sd^2/n_a) + (sd^2/n_b)]}$, where sd^2 = the variance of the source population (i.e., the square of the standard deviation); n_a = the size of sample A; and n_b = the size of sample B.

The SEM estimates can be checked by the use of a pooled standard deviation. Pooled standard deviation is a way to find a better estimate of the true standard deviation given several different samples taken in different circumstances where the mean may vary between samples but the true standard deviation (precision) is assumed to remain the same. The calculation proves to be a good estimate. The SEM provided by FOIA documents of 65 necessarily means that the SEM of the remaining subjects must be greater than the SEM, 141, for the baseline group comprising all subjects. This is exactly what the calculations determine. The standard deviation using the pooled standard deviation calculations above are 312 ± 160 (6) or 282 ± 180 (5). The numbers calculated are problematic for subject inclusion.

The study states subjects with untreated endocrine abnormalities were excluded. This includes hypogonadism. If the investigators included men with hypogonadism, than the research conditions are false. But the only mathematical condition under which one can have a group with 6 or 5 subjects and SEM cited above would be to have a subject that by biochemical parameters, serum total testosterone, is hypogonadal.

Using the optimal conditions for 6 subjects [312 ± 160 (6)], will result in a serum testosterone of 240 for 5 subjects and 672 for 1 subject. This alone is a highly improbable event, 240 for 5 subjects. Using the optimal conditions for 5 subjects [282 ± 180 (5)], will result in a serum testosterone of 200 for 5 subjects and 692 for 1 subject. Again, this is a highly improbable event, 200 for 5 subjects. Both serum testosterone values, 200 and 240, are hypogonadal levels. However, even assuming a lower value for hypogonadism, the likelihood of a hypogonadal value taking that 5 subjects having identical values is infinitesimal is very high. But for the subject exclusion to be true, the serum testosterone values provided by FOIA documents are false. These are only estimates and the only true representation for the data is that found in the study notes. The likelihood is good that there is falsification or fabrication of data, if the data presented is from the study subjects.

Discussed previously, the Ryan Commission recommendations for research misconduct were not accepted and the definitions currently applicable are those of falsification, fabrication, or plagiarism (FFP). Nevertheless, the studies presented in the book and notably this study demonstrates the dictates for a better and more inclusive definition.

As scientific misconduct hinges on the strict definitions for fabrication or falsification, the data will necessarily provide the proof for misconduct. While much of the evidence is circumstantial in nature it points to researchers attempting to hide, deny, and misdirect by any means possible that the subjects had anabolic steroid induced hypogonadism. An admission the subjects have anabolic steroid induced hypogonadism (ASIH) will by default show them to be in violation of 45 C.F.R. 46. Thus, these the researchers set out to demonstrate the subjects did not have ASIH. This is a steep and insurmountable goal when one considers the all of the available published literature uniformly demonstrates ASIH, both licit and illicit use. The only other possible manner in which to accomplish this was to fabricate and falsify data.

Allegation #4, #6-#14: In order to approve research the IRB shall determine that informed consent will be appropriately documented. The informed consent process for the research failed to include the elements required by DHHS regulations at 45 C.F.R. § 46.116. Informed consent deficiencies includes the failure to document accurately the duration of subject's participation, failure to document the foreseeable risks or discomforts to the subject, failure to document risks greater than minimal risk[432] that include failure to explain medical treatments for injury, failure to document risks of particular treatment to the subject, failure to document treatment costs for injury from treatment, failure to document consequences of withdrawal from research, and failure to provide subjects with information and findings that relate to the subject's willingness to continue participation.

Adherence to the consent requirement is not a guarantee of ethical research. Research may violate what is ethically acceptable even when consent has been granted. Of all requirements, none has received as much explication as informed consent. The purpose of informed consent to ensure that individuals control whether or not they enroll in clinical research and participate only when the research is consistent with their values, interests, and preferences. To provide informed consent, individuals must be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate.

The admitted lynchpin for the informed consent process is the presence or absence of hypogonadism after AAS cessation. This much is admitted to in the USC/CDU response, "In specific, it is alleged that since the research did not take in to account the possibility of the development of hypogonadism, the informed consent process failed."[433] Thus, whether the USC/CDU informed consent complies with the requirements of 45 C.F.R. § 46.116 is a simple inquiry as to the existence of anabolic steroid induced hypogonadism (ASIH).

Based upon USC/CDU reports, OHRP notes that an IRB could reasonably have made the determinations necessary for the approval of the research referenced above. In the USC response, the chairperson of USC IRB states, "Hypogonadism is not referenced by name because that is a medical term and the IRB does not permit the use of medical terminology without explanatory lay language."[434] This is error and brings into question as to whether the chairperson ever bothered to read the informed consent. In the section BACKGROUND of the informed consent, there is the clear use of the term hypogonadism. Included in the background is the following: "[v]ery low levels of testosterone in the blood (a disorder called hypogonadism)."[435] Tucked

amongst the FOIA documents, is an inquiry for loss of gains after AAS cessation obtained during AAS administration.[436]

If ASIH does not occur, than the USC/CDU response is the correct one and compliance with the informed consent regulations is not an issue. However, if ASIH occurs, than the USC/CDU response is in error, there is noncompliance with federal informed consent requirements. This is the case even if there is no publication demonstrating ASIH under the identical circumstances because the available published literature in existence does show ASIH, in fact, one-hundred percent of the time. The investigators responsibility is not to ignore and dismiss data that might alter the risk/benefit results but to include such data and more importantly, protect the safety of the patient.

The refusal to admit the development of hypogonadism after AAS cessation therefore results in USC/CDU admitting to no discussion or documentation of ASIH and all associated side effects (risks) from hypogonadism after AAS cessation. These would include failure to provide information relating to ASIH including dose-response studies on HPTA normalization, recognition ASIH is of unknown duration and severity, thereby preventing any discussion of the full extent and seriousness of ASIH, since the aforementioned studies of HPTA normalization have not been performed it is not possible to accurately state the duration of the subject's participation, failure to document greater than minimal risk, and costs relating to ASIH treatment.

The following statement from the IRB chair is frightening and surpasses all known levels of arrogance. "Nor were investigators required to investigate if hypogonadism occurred." The IRB, as well as the investigator, responsibility is to protect the human research subject from undue risk. Here, the IRB chairperson unequivocally states that if a known harm, hypogonadism, occurs with the drug treatment there is no responsibility on the part of the investigators to inquire further either to potential patient harm or to an adverse effect upon the data and the conclusions drawn thereof. Apparently, this includes even the reporting of hypogonadism. This statement, alone, is sufficient to demonstrate a violation, in principle, of federal statute 45 C.F.R. 46 Protection of Human Subjects.

It is inarguable that in medicine, an adverse effect is a harmful and undesired effect resulting from a medication or other intervention. An adverse effect or side effect (when judged secondary to a main or therapeutic effect) may result from an unsuitable or incorrect dosage or procedure (which could be due to medical error). Adverse effects are sometimes "iatrogenic" because they are physician/treatment generated. Some adverse effects only occur only when starting, increasing, or discontinuing a treatment. Adverse effects may cause medical complications of a disease or procedure and negatively affect its prognosis. They may also lead to non-compliance with a treatment regimen.

Indications of a harmful outcome is usually by some result such as morbidity, mortality, body weight alteration, enzyme levels, loss of function, or a pathological change detected at the microscopic, macroscopic, or physiological level. Other indications include symptoms reported by a patient. Adverse effects may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other disease.

DHHS regulations for the protection of human subjects contain specific requirements relevant to the review and reporting of adverse events and unanticipated problems. The definitions and reporting requirements for adverse events differ between Federal regulations. The notification requirements described in the Common Rule define adverse events as "unanticipated problems" involving risks to study participants or others.[437] The FDA defines adverse events as any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment.[438]

Federal regulations require written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to the IRB, appropriate institutional officials, and the Department or Agency Head. Under a different set of regulations, the FDA requires the sponsor to notify the FDA and participating investigators of any adverse event associated with the use of a test article that is "both serious and unexpected."

An effect that occurs in one-hundred percent of exposed individuals to a drug treatment is reason for concern. If the effect is anticipated, ignoring or dismissing of the effect requires an explanation beforehand for such an action. If the effect is unanticipated, reporting of the event is required under federal regulations. Further, consideration should be given to the unanticipated effect, the adverse event, and the impact or influence on the primary outcomes of the study, increase in risk of psychological or physical harm to the subject, and any change that needs to occur in the research design or methodology.

The response asserts, "Since the risk of hypogonadism had not been seen in similar previous studies using similar androgens, such risks were not required to be presented as part of the informed consent process."[439] The USC/CDU response demonstrates a steadfast refusal to recognize a period of hypogonadism after AAS cessation. The refusal is in the face of every peer-reviewed article investigating AAS and the HPTA ever published to show HPTA suppression after AAS cessation. The refusal is contrary to even the basic understanding of HPTA physiology taught in the most rudimentary medical school course. USC/CDU response to the informed consent allegations are from a position of fabricated ignorance and arrogance. It is an insult to believe that anyone with a semblance of common sense would believe these explanations but this is apparently the case by the OHRP determination letter.

11

SOLUTIONS

The clinical application of androgens in the treatment of various medical conditions has increased in the last decade. Because of the novelty of applying these agents, especially in wasting syndrome, investigations have focused largely on the anabolic actions and side effects during the course of therapy itself. To date, no consideration has been given to the endocrine status post-treatment, particularly development of iatrogenic (caused by the diagnosis, manner, or treatment of a physician) hypogonadotrophic hypogonadism. The negative impact of hypogonadism on physical and mental well-being should be of major concern for patients upon cessation of androgen therapy.

It has been documented that androgens and anabolic-androgenic steroids cause a negative feedback inhibition of the hypothalamic pituitary testicular axis.[440] To date, all compounds classified as either androgens or anabolic-androgenic steroids have been shown to suppress gonadotropin production as well as endogenous testosterone release. This is a characteristic of this class of medicines that has been virtually ignored in most clinical trials.[441] Although it is well understood that this effect does occur with androgens, the duration and severity of the condition is not. This bears repeating, the period of hypogonadism after androgen cessation is unknown as to duration and severity.

The few articles describing hypogonadotropic hypogonadism associated with androgens state that it is transient and insignificant have based their assumptions on measuring spermatogenesis.[442] These articles measured the return of spermatogenesis after cessation of androgens. This assumption is erred as medicine has already shown that spermatogenesis can be restored in the presence of hypogonadal testosterone levels.

Sequelae of hypogonadism may include adverse psychological changes (malaise, depression, decreased libido, etc.), erection dysfunction, osteoporosis, compromised immune system integrity, negative alteration in protein kinetics, decreased fat oxidation, increased body fat, loss of lean body mass, decreased strength, and more. Significantly, recent GnRH induced hypogonadism studies demonstrate an increased risk of heart attack and death. Interestingly, the OHRP complaint and corresponding FOIA documents (Chapter 10) show the occurrence of a heart attack within the first month after androgen discontinuation. In a shocking portrayal of

ignorance and ego, the investigators attributed this to nothing related to their study when a simple blood test for testosterone might have proven insightful.

Androgen therapy is an accepted treatment for HIV-related muscle wasting and observed with other medical disorders that include those in the prior chapters. In addition to the limited nature of the androgen treatment there are other attendant problems that may necessitate the cessation of androgens: polycythemia vera[443], elevated hepatic enzymes[444], and negative alterations in lipid profile[445] are a few of the causes.

What recourse or therapy is available if signs and symptoms of hypogonadism are severe and problematic? Reinitiating androgens will only continue to suppress the HPTA and potentially worsen the condition for which they were stopped. It is entirely possible, more likely probable, to place an individual on androgen therapy and then upon cessation to reverse all of the positive changes and actually continue to a state of worse ill-health due to anabolic-androgenic steroid induced hypogonadism.

Published studies utilizing anabolic-androgenic steroid (AAS) therapy have not addressed the effects of hypogonadism after androgen cessation. Indeed the case for scientific misconduct is strong. There is no doubt the researchers are well aware of anabolic-androgenic steroid induced hypogonadism. The study design, funding sources, and glaring absence of any mention of the effects of hypogonadism after androgen cessation are inexcusable. Of an even greater source for their heinous conduct is the disregard and ignoring for their own data! This results in a danger to the public health and welfare.

As an added insult to those that have gone before us is the blatant indifference to prior published studies. It is ironic and saddening that this clinical problem was published[446] in 1989 concerning hemodialysis patients only to go ignored in recently published studies.[447] In 1985, a study by Forbes et al. measured the sequence of body composition changes after twelve weeks of testosterone administration was discontinued.[448] They found that after two months, roughly half of the lean body mass gains attributed from the treatment were lost.

The recently published study of Schroeder et al[449] has been the first study with follow-up on the effects of androgens and body composition changes. After twelve weeks of oxandrolone administration, anabolic improvements were lost in the subsequent twelve weeks after discontinuing the androgen. Rather than recognize the readily obvious reason for the muscle loss the authors suggest, "**However, the benefits were lost within 12 wk after oxandrolone was discontinued, suggesting that prolonged androgen treatment would be needed to maintain these anabolic benefits.**" These results and bizarre explanation are a foreboding of what has taken place, is taking place, and will continue to take place until there is recognition of the importance for anabolic-androgenic steroid induced hypogonadism.

Following is a brief discussion on the treatment for anabolic-androgenic steroid induced hypogonadism. Hypogonadism is defined as "inadequate gonadal function, as manifested by deficiencies in spermatogenesis and/or the secretion of gonadal hormones."[450] Hypogonadism is structural, physiological, or functional. It is critical to exclude structural causes of hypogonadism prior to investigating whether the etiology is physiological or functional.

Physiological hypogonadism can be primary (testicular failure), secondary (hypothalamic-pituitary failure), or mixed. Luteinizing hormone (LH) should be measured to determine whether the cause is primary (hypergonadotropic hypogonadism) or secondary (hypogonadotropic hypogonadism). LH levels >10 indicate primary testicular failure whereas LH levels <2 suggest a hypothalamic-pituitary lesion. Levels within the normal range suggest an age-related, decreased hypothalamic response to declining testosterone levels.

If a low testosterone level has been established, further laboratory testing is used to determine whether the hypogonadism is related to a primary testicular disorder (hypergonadotropic hypogonadism) or to pituitary disease (hypogonadotropic hypogonadism). The primary feature of hypogonadotropic hypogonadism is the failure of a reciprocal increase in gonadotropins in the setting of a substantially decreased testosterone level. In patients with signs and symptoms indicative of hypogonadism, determining luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels together with the initial total testosterone level is usually most efficient.

Dynamic endocrine methodologies or challenge tests investigate HPTA functionality. These methods are useful in distinguishing physiological from functional hypogonadism. This is important because in the diagnosis of physiological hypogonadism the possibility of HPTA restoration is absent or minimal. A diagnosis of functional hypogonadism is an indication of HPTA functionality and restoration.

The medicines utilized for the protocol used to normalize the HPTA come from the scientific literature detailing treatments of portions of the HPTA axis. The individual use of human chorionic gonadotropin (hCG), clomiphene citrate, and tamoxifen in the diagnosis and treatment of testicular and hypothalamo-pituitary function are well-known, well-accepted, and well-tested standards of care treatments in peer reviewed medical literature.

The HPTA protocol designed by Dr. Scally uses the medications hCG, clomiphene citrate, and tamoxifen. The HPTA protocol results help reveal the underlying cause for hypogonadism but also determine HPTA functionality of the axis, both the testes and hypothalamo-pituitary, and further the possibility of HPTA restoration. Thus the HPTA protocol is a two-staged challenge test combined into a single treatment.

The first phase of the HPTA protocol examines the functionality of the testicles by the direct action of hCG.451 Human chorionic gonadotropin (hCG) is a polypeptide hormone produced by the human placenta, is composed of an alpha and a beta sub-unit. The alpha sub-unit is essentially identical to the alpha sub-units of the human pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as to the alpha sub-unit of human thyroid-stimulating hormone (TSH). The beta sub-units of these hormones differ in amino acid sequence. The action of hCG is virtually identical to that of pituitary LH, although hCG appears to have a small degree of FSH activity as well. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testis to produce testosterone.

hCG has been shown to significantly improve gonadal function in hypogonadotropic hypogonadal adult males.[452] Its use has proven beneficial in many clinical situations including

stimulation of testosterone and sperm production. Recently, a case study report used hCG successfully in ASIH.[453]

The increase in serum testosterone with the hCG stimulation is useful in determining whether any primary testicular dysfunction is present. An important consideration in the hCG stimulation test is the proper administration for both the dose and duration of hCG. This initial value is a measure of the ability of the testicles to respond to stimulation from the hCG. A failed dynamic challenge test with hCG is unable to produce total testosterone within the lowest 20% of the normal reference range for a male population 20-30 years, approximately 400 ng/dL. One of the major concerns amongst individual is so-called desensitization from excessive hCG administration. What is more likely is the inadequate amount of administration leading to a false negative impression. The literature does not support desensitization even at levels of 5,000 IU administered three times per week for two weeks. The typical optimal dose is in the range of 1,000 IU to 2,500 IU administered every other day.

The failure of the testes to respond to an hCG challenge is indicative of primary testicular failure. In the simplest terms, the first half of the protocol is determine testicular production and reserve by direct stimulation with hCG. If one is unable to obtain adequate (normal) levels successfully to the first half there is little cause or reason to proceed to the second half. Demonstration of HPTA functionality is by an adequate response of the testicles to raise the serum level of total testosterone into the normal range, equal to or greater than 400 ng/dL. If this is observed, the hCG is discontinued and the second phase of the HPTA protocol begun.

hCG's effect is centralized at the Leydig cells of the testicles and stimulates hormone function at the testicular level but does not reverse hypothalamic-pituitary suppression. Adequate stimulation from pituitary gonadotropins is required for the Leydig cells of the testicles to function independently in the body's normal hormone axis.

The second phase of the HPTA protocol, clomiphene and tamoxifen, examines the ability of the hypothalamo-pituitary to respond to stimulation by producing LH levels within the normal reference range.454 Gonadotropin-releasing hormone (GnRH) stimulation test has been used in the diagnosis of central precocious puberty (CPP) and in the differentiation of CPP from other causes of precocious puberty.[455] This test is sometimes useful for distinguishing hypogonadotropic hypogonadism. However, this test is done by intravenous injection, burdensome, and under acute conditions and loses its utility for sustained stimulation of the hypothalamo-pituitary.

The administration of antiestrogens is a common treatment in attempts to restore the HPTA because antiestrogens interfere with the normal negative feedback of estradiol at hypothalamic and pituitary levels. This effect increases endogenous gonadotropin-releasing hormone secretion from the hypothalamus and LH secretion directly from the pituitary.456 In turn, LH stimulates Leydig cells in the testes, and this leads to increased local testosterone production.

Clomiphene is a selective-estrogen receptor-modulator (SERM). Clomiphene citrate is a mixed estrogen agonist/antagonist. Clomiphene is a racemic mixture of zuclomiphene and

enclomiphene. Zuclomiphene has estrogen agonistic effects, while enclomiphene has estrogen antagonistic effects. Clomiphene exhibits no androgenic, antiandrogenic, or progestational effects, nor does it affect pituitary-thyroid or pituitary-adrenal function. Tamoxifen is a nonsteroidal estrogen receptor antagonist, 4-Hydroxytamoxifen being the active metabolite of tamoxifen.

Clomiphene citrate and tamoxifen compete with estrogen for estrogen receptor binding sites, thus eliminating excess estrogen circulation at the level of the hypothalamus and pituitary and allowing gonadotropin production to resume, raising FSH & LH levels and secondarily gonadal sex hormones. In the many years of prescribing this drug combination the occurrence of adverse side-effects were minimal. These were restricted to headaches or ocular complaints, resolved with decreasing the clomiphene dose.[457]

Clomiphene has been reported in a case study to reverse andropause secondary to anabolic-androgenic steroid use.[458] The patient received clomiphene citrate 50 mg twice per day in an attempt to raise his testosterone level. The patient when followed up after two months had a relapse, tiredness and loss of libido, after discontinuing clomiphene citrate. Guay has used clomiphene citrate as therapy for erection dysfunction and secondary hypogonadism. Patients received clomiphene citrate 50 mg per day for 4 months in an attempt to raise their testosterone level.[459]

The simultaneous use of clomiphene citrate and tamoxifen was determined through preliminary use of clomiphene citrate and tamoxifen, individually. It was discovered that although both clomiphene citrate and tamoxifen met with some success, when combined together they achieved a more significant increase in gonadotropin production. It was thought that the isomers of clomiphene partially counterbalanced each other out and the addition of tamoxifen resulted in a net additional antagonistic effect. This clinical outcome resulted in the combination therapy of clomiphene citrate and tamoxifen.

In the classical clomiphene citrate stimulation test, 100 mg per day is given for five to seven days. A doubling of LH and a 20% to 50% increase in FSH are normal results indicative of an intact hypothalamic-pituitary response.

This challenge test differentiates secondary hypogonadism, but also serves to stimulate or jump-start the hypothalamo-pituitary to begin a return to normal function. The physiological type of hypogonadism—hypogonadotropic or secondary—is characterized by abnormal low or low normal gonadotropin (LH) production in response to clomiphene citrate and tamoxifen. If there was a successful stimulation of testicular testosterone levels by hCG but an inadequate or no response in LH production than the patient has hypogonadotropic, secondary, hypogonadism. While, again, this is an ominous sign for return of HPTA functionality and restoration, future attempts might prove successful (see concluding paragraphs).

In the simplest terms, the second half of the protocol is to determine hypothalamo-pituitary production and reserve with clomiphene and tamoxifen. The administration of SERM leads to an appropriate rise in the levels of LH, suggesting that the negative feedback control on the hypothalamus is intact and that the storage and release of gonadotropins by the pituitary is normal. Long-term follow-up is necessary to ensure permanent reversal of hypogonadotropic

hypogonadal conditions, HPTA restoration, by the use of hCG, clomiphene citrate, and tamoxifen.

There are other drugs cited within published literature that might prove beneficial in ASIH. These include human growth hormone (hGH), aromatase inhibitors, and selective progesterone receptor modulators (SPRM).

A body of evidence suggests the existence of a relationship between growth hormone (GH) and the HPTA.[460] It has been suggested that rGH administration could improve testosterone production induced by CG alone or combined with gonadotropins. Patients treated with hGH and hCG found a significant increase in testosterone levels when compared with CG treatment alone.[461]

The aromatase inhibitors anastrozole (Arimidex) and letrozole (Femara) reduce estradiol levels by the inhibition of the enzyme producing estradiol. Studies demonstrate this to cause an elevation of the gonadotropins and secondarily serum testosterone. SPRM administration under certain conditions produces an elevation of gonadotropins, particularly FSH.

Following is a clinical evaluation of the combined, simultaneous use of hCG, clomiphene citrate, and tamoxifen citrate as a treatment option for ASIH. This observational analysis of the aforementioned treatment protocol assessed the efficacy of these medicines under non-controlled, non-randomized conditions. In our sample, combined pharmacotherapy was effective in restoring normal function of the HPTA.

There are three major clinical presentations: (1) eugonadal (normal testosterone) on presentation (i.e., obesity or wasting syndrome); (2) hypogonadal on presentation; and (3) eugonadal on presentation or after treatment, but with hypogonadal signs and symptoms. These groups are not meant to be inclusive for all individual presentations. In general, treatment will fall into one of the categories, but will necessarily require attention to individual medical conditions. It is clearly understood that other conditions that cause hypogonadism have been excluded prior to the initiation of treatment.

Treatment is divided into basically four points of clinical evaluation and laboratory testing that comprise three stages or phases: (1) diagnosis; (2) testes function; (3) hypothalamic-pituitary function; and (4) hypothalamic-pituitary testes function/restoration. Depending on the clinical evaluation and laboratory testing the patient will proceed onto the next stage in treatment.

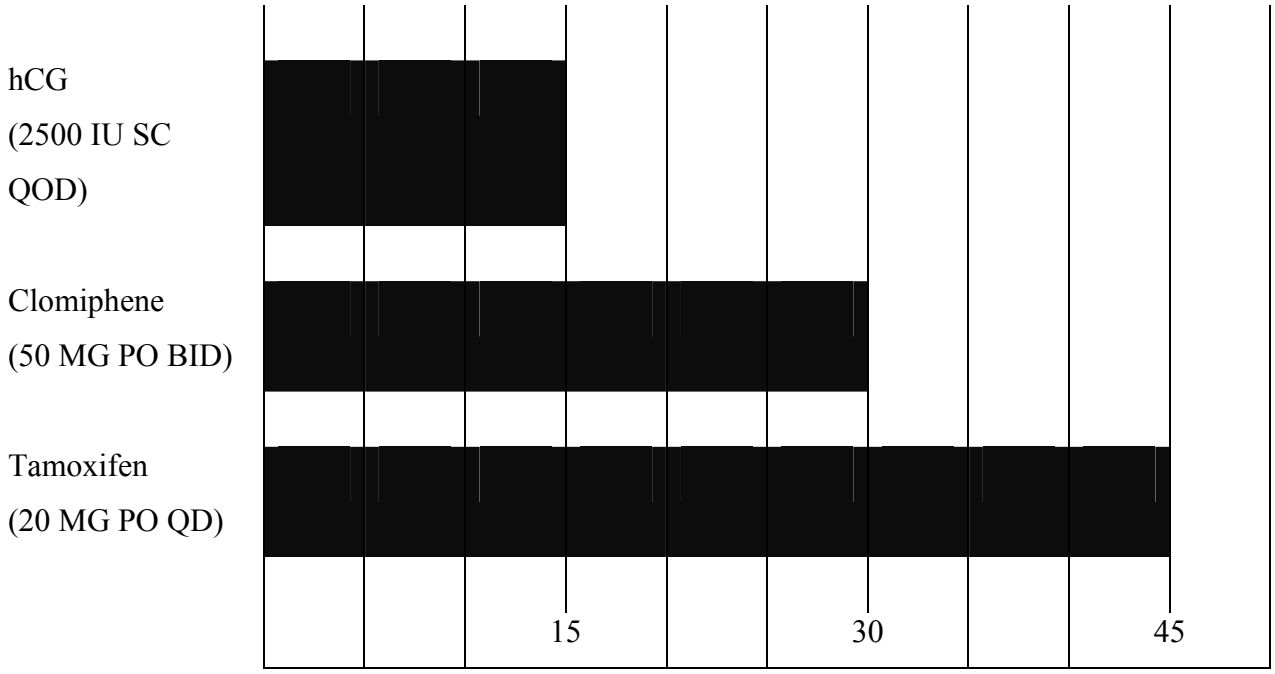
Combination Therapy of Human Chorionic Gonadotropin, Clomiphene Citrate, and Tamoxifen in the Treatment of Androgen Induced Hypogonadism: An Observational Study

Fifteen men who had self-administered nonprescription androgens presented with hypogonadotropic hypogonadism (total testosterone <241 ng/dl, luteinizing hormone, LH <1.5 mIU/ml). Patients received eugonadal status based upon both LH (>1.5 mIU/ml) and total testosterone (>241 ng/dL) values returning to normal. If these values remained subnormal at the

conclusion of the first 45 days of treatment, a second course was initiated (average treatment duration = 83 days +/-48). Blood work drawn at least two weeks after discontinuing all medications revealed an increase in total testosterone from 119.8 (+/-55.5) to 572.4 (+/-256.3) ng/dl ($p < .0001$) and an increase in LH from <1.00 to 6.67 (+/-5.13) mIU/ml ($p = .002$).

Treatment consisted of administration of (a) human chorionic gonadotropin, (b) clomiphene citrate, and (c) tamoxifen. Upon diagnosis, all medications started simultaneously with hCG (2500 IU subcutaneous every other day X eight injections), clomiphene citrate (50 mg orally twice per day X 30 days), and tamoxifen (20 mg orally once per day X 45 days). The administration timeline is shown graphically below. This protocol was repeated with every patient until serum LH and total testosterone values reached normal ranges.

Time Course of Medications (Days)



Hypothalamic Pituitary Gonadal Axis Normalization Protocol After Androgen Treatment

An uncontrolled study of 19 HIV-negative eugonadal men, ages 23–57 years, administered intramuscularly testosterone cypionate (200 mg/week) and nandrolone decanoate (200 mg/week) for twelve weeks. Approximately two weeks after the last injection treatment began with a combined regimen of hCG (2500 IU subcutaneous every other day X eight injections), clomiphene citrate (50 mg orally twice per day X 30 days), and tamoxifen (20 mg orally once per day X 45 days).

DEXA studies were performed prior to and on the completion of medications. Mean fat-free mass by DEXA increased from 64.1 to 69.8 kg ($p <0.001$); percent body fat decreased from 23.6 to 20.9 ($p <0.01$); strength increased significantly from 357.4 lb to 406.4 lb ($p = 0.02$). No significant changes in serum chemistries and liver function tests were found. HDL-C decreased

from a mean value of 44.3 to 38.0 ($p = 0.02$). Prior to androgen treatment, mean values for luteinizing hormone (LH) and total testosterone were 4.5 and 460, respectively. At the conclusion of the twelve week treatment with androgens the mean levels were LH <0.7 and total testosterone 1568. The mean values after treatment with the combined regimen were LH = 6.2 ($p < 0.001$) and testosterone = 458 ($p < 0.001$).

Improvements in Body Composition in Obese HIV-Infected Men with Androgen Therapy Followed by Selective Estrogen Receptor Modulator Treatment (SERM)

A case study of 2 HIV-positive eugonadal men with over 25% total body fat, both age 45 years, who complained of increased abdominal fat after initiation of HAART. They were administered intramuscular testosterone cypionate 100 mg/week and oral oxymetholone for 12 weeks. Oxymetholone dose was initiated at 50 mg/day, increasing by 50 mg/day each four weeks for a maximum final dose of 50 mg/three times per day. Administration of clomiphene citrate (50 mg PO twice daily X 60 days) and tamoxifen (10 mg PO twice daily X 60 days) was started after androgens. Each individual carried out their self-prescribed exercise and diet plan.

All laboratory studies and body composition measurements by DEXA were done at baseline and one month after completion of medications. In the first individual body weight increased 88.1 kg to 89.5 kg, lean body mass increased 62.3 kg to 71.4 kg, and body fat decreased 22.1 (26.2%) kg to 14.4 (16.7%) kg. In the second individual body mass decreased 94.8 kg to 91.5 kg, lean body mass increased 59.5 kg to 63.4 kg, and body fat decreased 32.3 (35.2%) kg to 24.9 (28.2%) kg. The baseline values for luteinizing hormone/total testosterone were normal at 7.0/414 and 4.2/365 prior to androgen treatment. One month after the conclusion of SERM, the values also normal at 5.3/407 and 3.6/512. No irreversible increases in liver enzymes over 3X upper limit were observed and both patients reported good quality of life (QOL) through the observation period. Neither one reported increased lipoatrophy during the treatment period.

Without any intervention, ASIH occurs every time following the cessation of administered exogenous AAS. The consequences of HPTA suppression after androgen cessation is the patient will become hypogonadal and suffer hypogonadism. Androgen induced HPTA suppression causes a severe hypogonadal state in most patients that often require an extensive period of considerable duration for normalization. This prevents most if not all individuals from discontinuing these medications.

In the functional type of hypogonadism, the ability to stimulate the HPTA to produce LH and testosterone levels within the normal reference range occurs. As hCG's effect is centralized at the Leydig cells of the testicles, clomiphene citrate and tamoxifen act upon the hypothalamic-pituitary region in stimulating gonadotropin production. The normal operation of both the testicular and hypothalamic-pituitary regions is crucial in returning HPTA function to normal.

It is the authors' opinion that returning one component of the axis to normal without returning the other would inhibit the operation of the entire HPTA and prolong dysfunction. It was with this understanding that hCG was combined with clomiphene citrate and tamoxifen as attempted therapy to reverse gonadal suppression. In the case of decreased testicular function

manifested by low testosterone levels, it is of primary importance to first return the normal function of the testicular cells.

These medicines hCG, clomiphene citrate, and tamoxifen, with each being given over a defined period and for specific but related problems. The successful restoration of the HPTA requires the medications to be taken as prescribed. hCG needs to be at a dose sufficient to stimulate testicular testosterone production. Also, the schedule for hCG is determined by when your own body should be attempting to produce its own testosterone. This is the ideal situation when AAS cessation date is known along with the type and dose of AAS being prescribed or taken.

The factors considered in this assessment of HPTA normalization—functionality—restoration are the degree each arm of the axis responds to the HPTA protocol, timing of the protocol after AAS cessation to avoid the occurrence of ASIH, clinical symptomatology, and other objective measurable parameters. A successful HPTA challenge, normalization, does not indicate HPTA restoration and long-term monitoring and follow-up are necessary, at a minimum, to ensure HPTA status.

HPTA restoration goal is returning the patient to a feeling of well-being or health. HPTA restoration affects a cure whereby the individual no longer requires treatment while hypogonadism, andropause, or HPTA dysfunction requires a commitment for life-long therapy. Monitoring afterwards is to ensure HPTA normalization—functionality has not reverted to HPTA dysfunction or hypogonadism. Patients treated with only the HPTA protocol that obtains normalization—functionality may eventually relapse and become hypogonadal.

AAS prescribing is for resolution of hypogonadal symptoms and sequelae. The HPTA normalization protocol is to for normalization—functionality of the HPTA axis. The HPTA protocol and AAS protocol are complementary therapies focused on HPTA normalization—functionality—restoration. The use of AAS, alone, or the use of HPTA, alone, is not a therapy for HPTA restoration with problematic ASIH.

The only known exception to ASIH after AAS cessation in the medical and scientific literature is the HPTA protocol developed by Scally.462 [463] The direct clinical care of over one thousand patients has formed the basis for the treatment of patients regarding hypothalamic pituitary testicular axis restoration (HPTA). Dr. Scally has presented and published findings on the minimization, elimination, and prevention of hypogonadism (AIH) after AAS cessation and the use of AAS with the HPTA protocol. These findings and studies are in the peer-reviewed medical literature for the greater medical community,[464] [465] including The Endocrine Society,[466] American Association of Clinical Endocrinologists,[467] American College of Sports Medicine,[468] and the International Society for Antiviral Research.[469]

The published literature either cites use of AAS or stimulating endogenous AAS production as treatments. Clomiphene citrate and tamoxifen act to raise sex hormones secondarily through the elevation of the gonadotropin LH. hCG raises sex hormone levels directly through the stimulation of testis. The commonality between hCG, clomiphene, and tamoxifen treatments is increased endogenous production of testosterone.

The androgen receptor (AR) is the critical link common to either exogenous AAS prescribing or increased endogenous AAS production. Any effective treatment for the hypogonadal symptoms and sequelae of ASIH will necessarily influence an upregulation and production of AR. In HPTA restoration patients, AAS dose and AAS duration prescribing of the proceeding are similar to AAS prescribing that increases AR. AAS have been proven as treatments in the signs and symptomatology of hypogonadism and to increase AR levels.

The best evidence that the treatment works is the overwhelming success in case after case. While this theory requires further substantiation in well-controlled trials, recent evidence lends some credibility to the androgen receptor possibly being a factor in HPTA restoration. In 2007, a study in the NEJM reveals the reversal of idiopathic hypogonadotropic hypogonadism after cessation of testosterone therapy in a significant, 20%, number of males with the disorder, including normosmic idiopathic hypogonadotropic hypogonadism (non-Kallmann syndrome).[470] [471] All patients who underwent reversal had testosterone levels similar to those in a cohort of healthy adult men.

The authors suggest, "There are practical implications of this observation. We would suggest that patients with idiopathic hypogonadotropic hypogonadism, with or without anosmia and regardless of their previous pubertal development, should be informed of the possibility of fertility and the spontaneous reversal of hypogonadism. In addition, men with idiopathic hypogonadotropic hypogonadism should be reassessed for recovery of the hypothalamo–pituitary–gonadal axis."

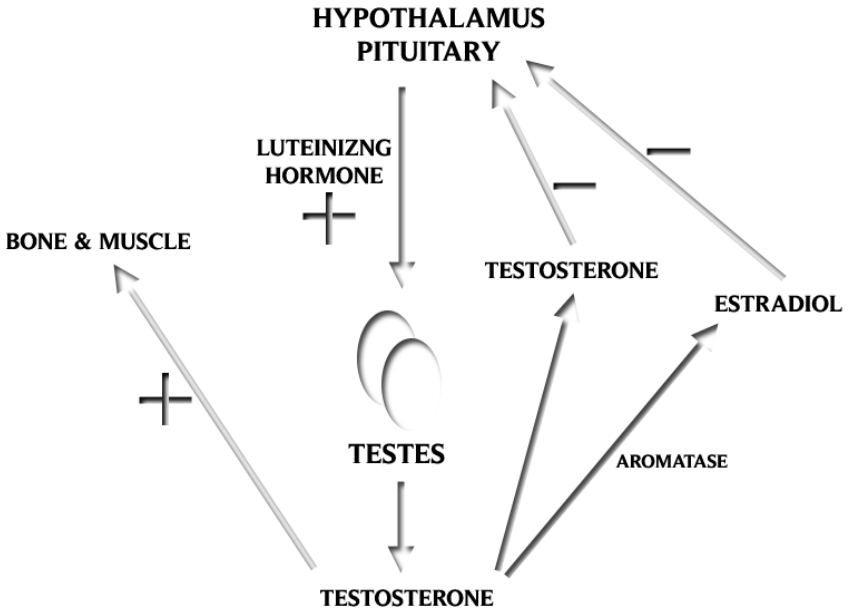
In discussing the possible mechanism the paper states, "Episodic secretion of GnRH from the hypothalamus is a key requirement for the initiation and maintenance of a normal reproductive axis in humans. However, the factors modulating the secretion of this hormone remain poorly understood." Moreover, "The number of neurons producing GnRH in the human hypothalamus is relatively small (<2000), and these neurons are distributed as a diffuse network, rather than as a discrete nucleus.[472] Such anatomy may render the GnRH pulse generator functionally vulnerable to minor perturbations, leading to GnRH deficiency and hypogonadotropic hypogonadism."

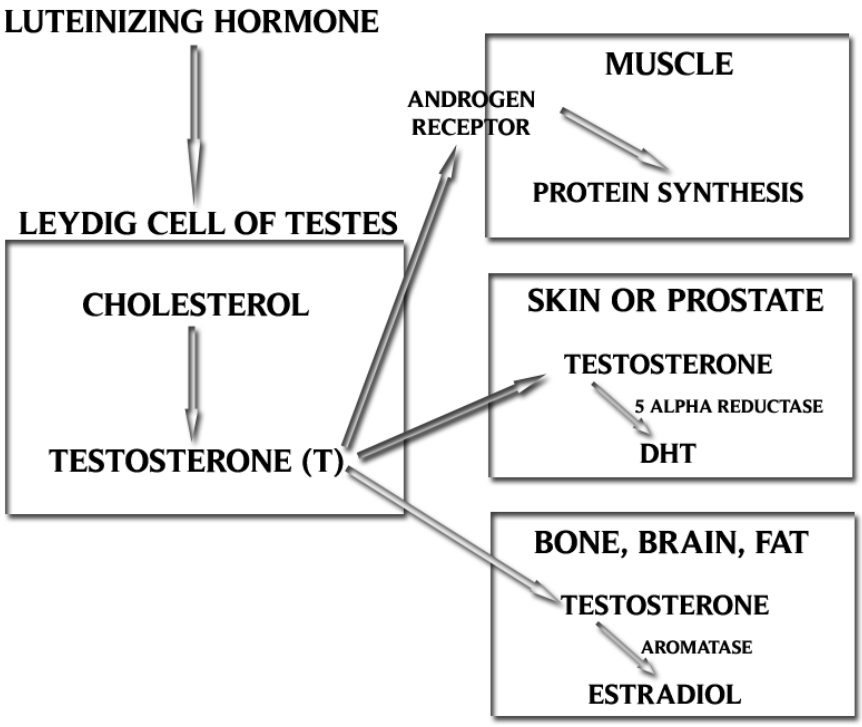
"Although the precise mechanism of reversal of hypogonadotropic hypogonadism is unclear, the mechanism may involve plasticity of the GnRH-producing neurons in adulthood. Plasticity, defined as the ability of the nervous system to adapt in response to the environment, is a striking feature of the vertebrate brain. We therefore speculate that sex steroids enhance the plasticity of the neuronal network producing GnRH in the adult human brain, leading to reversal of hypogonadotropic hypogonadism."

The problems of anabolic-androgenic steroid research present a unique and valuable opportunity. The solution to the problem of anabolic-androgenic steroid induced hypogonadism makes available treatments for the adverse psychological effects of anabolic steroid cessation, both prescription and nonprescription, previously incorrectly attributed to dependency or addiction, combinatorial therapy with androgens for wasting conditions without the attendant hypogonadism, combinatorial therapy with androgens for obesity, and mitigation of future post male contraceptive infertility.

APPENDIX A

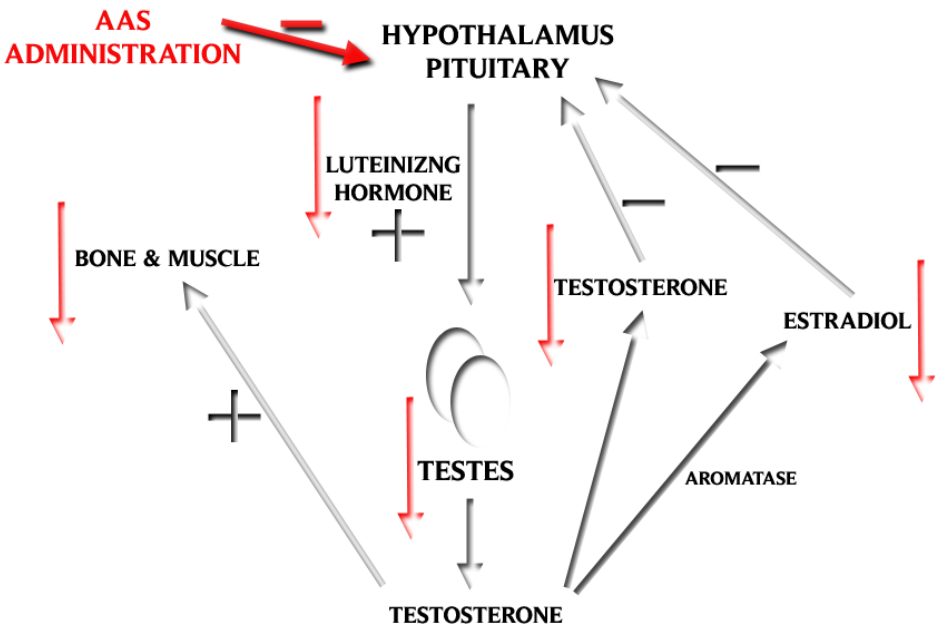
HYPOTHALAMIC PITUITARY TESTICULAR AXIS (HPTA)

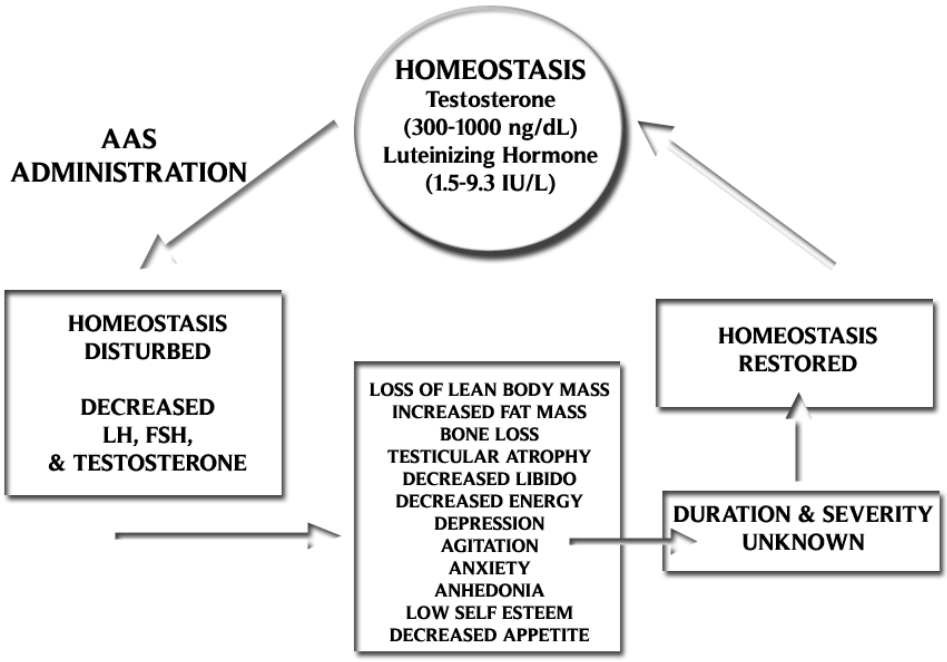



LUTEINIZING HORMONE
LEYDIG CELL OF TESTES
CHOLESTEROL
TESTOSTERONE (T)
ANDROGEN RECEPTOR
MUSCLE
PROTEIN SYNTHESIS
SKIN OR PROSTATE
TESTOSTERONE
5 ALPHA REDUCTASE
DHT
BONE, BRAIN, FAT
TESTOSTERONE
AROMATASE
ESTRADIOL

APPENDIX B

ANABOLIC STEROID ADMINISTRATION & HPTA




HOMEOSTASIS
Testosterone
(300-1000 ng/dL)
Luteinizing Hormone
(1.5-9.3 IU/L)
AAS
ADMINISTRATION
HOMEOSTASIS
DISTURBED
DECREASED
LH, FSH,
& TESTOSTERONE
LOSS OF LEAN BODY MASS
INCREASED FAT MASS
BONE LOSS
TESTICULAR ATROPHY
DECREASED LIBIDO
DECREASED ENERGY
DEPRESSION
AGITATION
ANXIETY
ANHEDONIA
LOW SELF ESTEEM
DECREASED APPETITE
HOMEOSTASIS
RESTORED
DURATION & SEVERITY
UNKNOWN

APPENDIX C

FREEDOM OF INFORMATION ACT (FOIA) DOCUMENTS

On June 16, 2003, a complaint was filed with the Office for Human Research Protections (OHRP), listing a series of allegations for violations of 45 C.F.R. 46 Protection of Human Subjects, Subpart A in a published study funded by public sources. The study of the OHRP complaint is, "Effects of an oral androgen on muscle and metabolism in older, community-dwelling men."[473] The complaint named the Departments of Medicine, Radiology, and Biokinesiology, Keck School of Medicine, University of Southern California, Los Angeles, California and Division of Endocrinology, Metabolism, and Molecular Medicine, Charles Drew University School of Medicine, Los Angeles, California.

The OHRP reviewed the University of Southern California's (USC) August 21, 2003 report and Charles R. Drew University School of Medicine and Science's (CDU) August 25, 2003 and September 27, 2004 reports, submitted in response to OHRP's July 9, 2003 and August 11, 2004 letters and made a determination regarding the referenced research. On November 5, 2004, OHRP published the determination letter, accessible at the OHRP website, regarding the complaint.[474]

OHRP maintains a list of "compliance determination" letters on their website.475 OHRP has implemented a practice to redact from compliance oversight determination letters posted on its website any sections that discuss unresolved concerns, questions, or allegations related to an ongoing investigation. Anyone wishing to request an unredacted copy of these letters should submit a request for the unredacted letter under the Freedom of Information Act (FOIA).

On January 4, 2005, a FOIA request was sent for documents pertaining to the above referenced complaint. In June 2006, the FOIA request resulted in receipt of scattered and incomplete documents regarding the OHRP complaint. The FOIA request was resubmitted but to date no other documents have been received. Following are documents from the FOIA request.

LAC+USC

Memorandum

Telephone 213-343-8288
Facsimile 213-226-2083
E-Mail fsattler@hsc.usc.edu

DATE: June 23, 2000

TO: Darcy Spicer, MD

FROM: Fred Sattler, MD

RE: **Post-study Adverse Event in a Subject Participating in Study 994040**

This is to report an Adverse Event occurring approximately four weeks after the study subject completed 12 weeks of study therapy on May 17, 2000. On June 13, 2000 his primary physician ([redacted]) called and informed me that subject [redacted] had just been hospitalized with an acute MI and renal impairment. After reviewing the events of the study and results of laboratory tests done on May 18, 2000 (attached), [redacted], Dr. Bhasin (Co-principal investigator for the project), and I felt that it was very unlikely that the study interventions were related to the adverse events.

At baseline, the subject was relatively asymptomatic with no evidence of active coronary artery disease and met eligibility criteria including a treadmill stress test, which showed no ischemia. There was a chronic right bundle branch block. The subject had impaired activities of daily living and used a walker for what appeared to be Parkinsonian like movements. During the course of the study, his muscle strength and functional performance improved and he donated his walker to a convalescent care facility.

At his last study visit on May 18, 2000, he was aymptomatic, there were no new physical findings, and his blood pressure was unchanged (167/84 mm Hg). He performed a VO2max test without problems or symptoms. His laboratory tests from that day showed slight increases in liver tests (ie bilirubin of 1.3, AST 52, and ALT 69). However, his serum BUN and creatinine were normal (11 and 1.0, respectively) as were the electrolytes. Moreover, the hematocrit had not increased in response to study therapy, ie 50.0% on 5-23-00 and 51.6% during screening on 1-21-00 (attached). Thus, there was no evidence that intravascular volume had increased in response to therapy.

Thus, after a careful review, the protocol team and I doubt that the heart attack occurring almost 4 weeks after completion of study therapy was related to the androgen being studied (we do not know if subject received active therapy or placebo) or to the strength testing.

Attachments:
cc: Shalender Bhasin, MD
Luis Mendez

55

Adverse Event Local Medical Reviewer Form

ADVERSE EVENT/DATE:

NAME OF STUDY:

PRINCIPAL INVESTIGATOR: Swalen den Bleyzin

REVIEWER SIGNATURE: George A Marks Jr

DATE: 02/07/2001

DISPOSITION and/or CONSIDERATIONS:

- ☐ Not related to the study
- ☐ Probably related to the study
- ☐ Related to the study
- ☐ Considered a serious AE
- ☐ Request further information
- ☐ Recommendations to IRB for protocol and consent form changes

COMMENTS:

Summary Sheet of 34 Deaths ~~not~~ 18 of which seem unrelated to Oxymetholone use. 16 are unknown one event reported from USC - Acute MI about 4 weeks after completion of treatment - Oxymetholone probably not related.

no need to stop Project.

FOIA#003

NT 003

Trailer #25, Unit 1
1200 North State Street
Los Angeles, CA 90033
Phone: 323-223-2340/2349
Fax: 323-224-8389

Health Sciences Campus
LAC+USC Medical Center and
Health Research Association

ADVERSE EVENT

The Report of Internal Adverse Event (AE) must be submitted, along with any other relevant information, to the IRB promptly and in no case later than five (5) business days following the time it becomes known the subject in your study suffered the unexpected AE. If an AE eventually proves fatal, the IRB must be notified within 24 hours.

Any unexpected AE which is related or possibly related to the drug, device or intervention must be reported regardless of whether or not the event is serious. The investigator should not report unrelated AEs and AEs judged to be the result of progressive disease.

The IRB relies a great deal on the expertise of the investigators to assess the report of the AE. Therefore, we need the principal investigator's advice concerning: the relationship of the AE to the drug, device or intervention; whether or not a change in protocol is necessary to minimize risks; and whether or not information about the AE justifies changes in the consent and/or re-consent of subjects already enrolled. The investigator is also asked to provide the rationale for the determination which helps the IRB to better understand the investigator's assessment of the significance of the AE in terms of human subject protection. The information about the AE may not be complete at the time of reporting; this should be reflected in the assessment. In order to facilitate IRB review of the AE and to avoid unnecessary delays, please ensure that each applicable section of the AE form is completed according to the instruction.

AEs that occur during research conducted at unaffiliated study sites should be reported to the IRB on the Report of External Adverse Event form.

IRB number: **994040**	Submission date: **June 23, 2000 via memorandum to Dr. Spicer**
TITLE OF PROJECT: Enter the title of the research project. **Investigator Initiated Dose Ranging Study of Oxymetholone in Frail Elderly Men: A Phase I/II Proof of Concept Study**	

PRINCIPAL INVESTIGATOR	**Fred R. Sattler, MD**		**323-343-8288**
SUBJECT **DD**	[redacted]	Date: **June 13, 2000**	Location: **Hawthorne, CA**

NATURE OF ADVERSE EVENT	Check all that apply. Serious Adverse Event	
DESCRIPTION OF THE EVENT	This subject completed study therapy and had his last evaluation on May 17, 2000. On June 13, 2000, his primary physician, [redacted], called and indicated that the subject had just been hospitalized with an acute heart attack and renal impairment.	
TREATMENT OF THE SUBJECT	Study Subject was admitted to the coronary care unit of the local hospital.	
OUTCOME	Describe the subject's outcome and prognosis. Not know at this time.	
RISK-BENEFIT REMAINS ACCEPTABLE:	☐ X Yes ☐ No	In your judgment is the overall risk-benefit relationship of the research still acceptable in light of the information concerning this adverse event report? If YES, then provide a brief rationale. [redacted], Dr. Shalendar Bhasin (co-principal investigator) and I felt that it was very unlikely that the heart attack was related to the study interventions. At baseline, the subject was relatively asymptomatic with no evidence of active coronary artery disease and he met all eligibility criteria including a VO2max/treadmill stress test, which showed no ischemia. The subject had impaired activities of daily living and used a walker for what appeared to be Parkinsonian-like movements. During the course of the study, his muscle strength and functional performance improved to the degree that he donated his walker to a convalescent care facility.

SCHOOL OF MEDICINE

Telephone 323-343-8288
Facsimile 323-226-2083
E-mail fsattler@hsc.usc.edu

AIDS Clinical Trials

Division of Infectious Diseases

Fred R. Sattler, MD
Professor Medicine

DATE: August 20, 2001

TO: Darcy Spicer, MD
Institutional Review Board

FROM: Fred R. Sattler, MD

RE: **Post Study Adverse Event (Project #994040)**

The IRB correspondence from 8/17/01 (action date 8/7/0) requested a narrative assessment as to why the principal investigator does not think that androgen therapy increases the risk for cardiac disease. In the context of the subject in question (original correspondence, June 23, 2000), we do not believe that participation in this study contributed to the subject's heart attack one month after completing study therapy for the following reasons:

Androgens might increase the acute risk for a heart attack by one of the following mechanisms:

1. By increasing intravascular volume, which might increase cardiac work or blood pressure. In this patient, there was no evidence of volume overload based on physical examination that showed no evidence of a new cardiac gallop, lung rales, neck vein distention or peripheral edema. Also, there was no increase in blood pressure during the course of study therapy.
2. By increasing hematocrit, which might increase blood viscosity. In this case the hematocrit decreased somewhat from 51.6% at baseline to 50.0% at the end of study therapy.
3. By increasing strength and physical activity, this could increase cardiac workload. Although lean tissue and muscle strength increased in this subject, his VO2max test, a rigorous treadmill stress test with 12-lead EKG monitoring, at baseline and then again at week 12 (end of therapy), showed no evidence of cardiac ischemia (ie, there was no flat or down sloping of the ST segments). Thus, we doubt that his becoming more active (discontinued use of his walker as described in the internal AE) contributed to the event.

Androgens may also adversely affect lipids. In this case the total cholesterol increased from 158 t· 183 mg/dL. The most consistent change with androgens are

University of Southern California
5P21 Clinic
1300 North Mission
Room 351
Los Angeles,
California 90033
Tel: 213 343 8288
Fax: 213 226 2083
e-mail:
fsattler@hsc.usc.edu

FOIA#005

ARCH COMMITTEE
Trailer #25, Unit I
FAX (213) 224-8389
PRE-REVIEW FORM

Return by: 4/14/99

that another reviewer may be assigned.

C-15

Pre-reviewer: Melinda Hurst

TITLE OF PROJECT: INVESTIGATOR INITIATED DOSE RANGING STUDY OF OXYMETHOLONE IN FRAIL ELDERLY MEN: A PHASE I/II PROOF OF CONCEPT STUDY

NAME OF PRINCIPAL INVESTIGATOR: Fred R Sattler, M.D.

Overall rating: ☐ Good ☐ Average ☐ Poor ☐ Should not be done

CRITIQUE AND COMMENTS NOT REQUIRING RESPONSE:

STIPULATIONS AND COMMENTS REQUIRING RESPONSE:

UNDER RISKS:
The informed consent states very clearly the serious nature of the risks involved. The list of possible damages that can be caused by Oxymetholone is impossible to assess without some indication of the % of incidents or the frequency of the conditions happening.
In a 12 week study period could cancer of the prostate develop? Could it be detected and identified with the study drug? The same for liver tumors. If these are possibilities it seems too dangerous for healthy men to undertake.

If, on the positive side, the men taking the steroid show marked gains will these be lost when the study ends?

Potential participants definitely need more statistical information in order to make anything like an informed decision.

FOIA DOCUMENT 005

Attach additional pages if required.
May a copy of this form be made available to the investigator? ☐ Yes ☐ No

APR-12-1999 05:17 PM

FOIA#006

CHARLES R. DREW
UNIVERSITY OF MEDICINE & SCIENCE

Division of Endocrinology,
Metabolism and Molecular Medicine

June 2, 2000

To: Jocelyn T. Whiten, Ph.D.
Chair, Institutional Review Board

From: Shalender Bhasin, M.D.

Re: Protocol, "Dose Ranging Study of Oxymetholone in Frail Elderly Men: A Phase II Proof of Concept Study" (A double-blind study)

This letter is to inform the IRB of an Adverse Event which occurred to one of the subjects [redacted], who is in the aforementioned protocol. The subject had follow up labs for week #6 which showed an elevation in the cholesterol (327mg/dl, normal ranges: 120-240 mg/dl). The patient's baseline cholesterol was slightly elevated at 259. Repeat cholesterols were done here at MLK/Drew lab on 5/3/00 and 5/16/00. These levels were 429 and 435, respectively.

Also, the subject's liver enzymes (ALT and AST) were elevated on 5/3/00 at 132, ALT, and AST 84. These were repeated on 5/11/00 and were 148, ALT, and AST 76. The enzymes were repeated again on 5/15/00 and were down to ALT 110 and AST 62.

The patient has been asymptomatic except for recent complaints of decreased libido. Although marked elevation cholesterol has not been shown to be a side effect of Oxymethalone, because of the patient's complaints of decreased libido and recent elevation of liver enzymes, it was decided to discontinue treatment. The patient will be out of town until after 6/5/00, but he has been advised to return to the Clinical Trials Unit for a follow up visit, physical exam, and repeat measurements of liver enzymes, and plasma lipids.

I have discussed this adverse experience with Dr. Fred Sattler, the P.I. of the study at LA-USC. He reviewed the laboratory data on nine subjects enrolled at LA-USC, and noted that only one patient had mild AST and ALT elevation. None of the patients showed any significant cholesterol elevation. We have not amended the consent form because elevation of liver enzymes was already listed as a potential adverse event in the consent form.

The appropriate staff at Unimed Pharmaceuticals has been notified of this event. If you have any further questions, please contact me at 323.563.9353.

Sincerely,

Shalender Bhasin, M.D.
Chief, Division of Endocrinology
Professor of Medicine
Charles R. Drew University

FOIA DOCUMENT 006

322

CC: Sandy Faulkner, R.N., Unimed Pharmaceuticals, Inc.

1731 East 120th Street, Los Angeles, California 90059 Telephone: (323)563-9353 Fax: (323)563-9352

FOIA#007

UNIVERSITY OF MEDICINE & SCIENCE

Division of Endocrinology,
Metabolism and Molecular Medicine

35

June 2, 2000

To: Jocelyn T. Whiten, Ph.D.
Chair, Institutional Review Board

From: Shalender Bhasin, M.D.

Re: Protocol, "Dose Ranging Study of Oxymetholone in Frail Elderly Men: A Phase II Proof of Concept Study" (A double-blind study)

This letter is to inform the IRB of an Adverse Event which occurred to one of the subjects [redacted] who is in the aforementioned protocol. The subject had follow up labs for week #6 which showed an elevation in the cholesterol (377mg/dl, normal ranges: 120-240 mg/dl). The patient's baseline cholesterol was slightly elevated at 259. Repeat cholesterols were done here at MLK/Drew lab on 5/3/00 and 5/16/99. These levels were 429 and 435, respectively.

Also, the subject's liver enzymes (ALT and AST) were elevated on 5/3/00 at 132, ALT, and AST 84. These were repeated on 5/11/00 and were 148, ALT, and AST 76. The enzymes were repeated again on 5/15/00 and were down to ALT 110 and AST 62.

The patient has been asymptomatic except for recent complaints of decreased libido. Although marked elevation cholesterol has not been shown to be a side effect of Oxymethalone, because of the patient's complaints of decreased libido and recent elevation of liver enzymes, it was decided to discontinue treatment. The patient will be out of town until after 6/5/00, but he has been advised to return to the Clinical Trials Unit for a follow up visit, physical exam, and repeat measurements of liver enzymes, and plasma lipids.

I have discussed this adverse experience with Dr. Fred Sattler, the P.I. of the study at LA-USC. He reviewed the laboratory data on nine subjects enrolled at LA-USC, and noted that only one patient had mild AST and ALT elevation. None of the patients showed any significant cholesterol elevation. We have not amended the consent form because elevation of liver enzymes was already listed as a potential adverse event in the consent form.

The appropriate staff at Unimed Pharmaceuticals has been notified of this event. If you have any further questions, please contact me at 323.563.9353.

Sincerely,

Shalender Bhasin, M.D.
Chief, Division of Endocrinology
Professor of Medicine
Charles R. Drew University

FOIA DOCUMENT 007

347

CC: Sandy Faulkner, R.N., Unimed Pharmaceuticals, Inc.

1731 East 120th Street, Los Angeles, California 90059 Telephone: (323)563-9353 Fax: (323)563-9352

CHARLES R.
DREW
UNIVERSITY OF MEDICINE AND SCIENCE
1731 East 120th Street, Los Angeles, California 90059

CONSENT FOR PARTICIPATION IN RESEARCH

Investigator Initiated Dose Ranging Study of Oxymetholone in Frail Elderly Men: A Phase II Proof of Concept Study. (A study to determine the correct dose of oxymetholone, a hormone which has an effect on muscles, in older men.)

Principal Investigator:
Shalender Bhasin, M.D.
Division of Endocrinology
1731 East 120th Street
Augustus F. Hawkins Bldg.
Los Angeles, CA 90059
323.563.9353

Co-Investigator:
Atam B. Singh, M.D.
Division of Endocrinology
1731 East 120th Street
Augustus F. Hawking Bldg.
Los Angeles, CA 90059
323.563.9353

You are being asked to be a subject in a research study about oxymetholone and its effects on muscles in older men which is being conducted by Shalender Bhasin, M.D. and Atam B. Singh, M.D., Division of Endocrinology, at Charles R. Drew University (CDU) and by Fred Sattler, M.D., at LA-USC. You have been asked to participate in the research because you are a male between the ages of 65-80 years old, able to eat a special diet (which a dietician will recommend during the study), and able to comply with the requirements of the study.

Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

- **Background and General Purpose of Study**

The purpose of this study is to determine if the medicine, oxymetholone will improve your muscle strength, physical performance (i.e. walking and stair climbing), lessen the amount of stomach fat, improve your sense of well being..

The study hopes to show that the use of oxymetholone will lessen the loss of muscle, which is the main reason for loss of physical strength in the older men.

The loss of muscle mass as you grow older is a complex process and involves a number of different things, such as your genetic make-up, lifestyle factors, what kind of disease you may have and hormonal changes in your body. There is some evidence that male hormone (testosterone) and related drugs such as oxymetholone can increase lean tissue in older men. This study plans to study the effects of oxymetholone on muscle mass and function. One reason for doing this research study is that muscle loss that occurs in old age increases the risk of fall and injury, causes loss of mobility and independence, and is associated with psychological depression due to dependency on others for daily living.

You will be one of fifteen men participating in this study at King-Drew Medical Center. King-Drew is one of two centers involved in this study. A total of thirty-six patients in the United States will participate in this two-center study being sponsored by Unimed.

- **Procedures**

Your participation in this research study will last for 14 weeks and include 6 clinic visits to the Clinical Research Center (CRC) at Drew University during the course of this study.

During your first visit (screening visit or visit 1), you will be asked to give informed consent to participate in the study, and 2 1/2 tablespoons of blood will be taken from your vein (needle puncture into a vein and blood withdrawn) for a number of different blood tests. The dietitian will advise you on what kind and how much food you should eat during this study. The results of the screening visits will determine if you will qualify to continue in the study. If you would like us to discuss your participation in this trial and/or medical care with your primary physician, we will ask you to sign a medical information release form.

After you qualify on the basis of the screening visit to participate in the research study, you will be asked to return in two weeks for clinic visit 2. You will be asked to keep a record of what you eat for three days before returning for this visit. During that time, you will have a full medical history, full physical examination, vital signs (blood pressure, heart rate, temperature), height and weight, 12-lead electrocardiogram (EKG, which measures the electrical activity of your heart), a chest x-ray (taking a picture of your chest with a special machine), and a motorized treadmill test. If you pass the screening tests, at visit 2 you will have a magnetic resonance imaging (MRI) scan (special machine to take a picture of your stomach and one leg) and a DEXA scan (a special X-ray of your body) which determines the lean mass and fat mass of your body.

The treadmill test will take less than 20 minutes. During this test you will breathe through a mouth piece and wear a nose clip so that all of your air can be collected and the amount of oxygen that you use during the exercise can be determined. The treadmill test will begin at a walking speed that is comfortable for you. During this time, the speed will be kept constant while the incline (similar to moving up a hill) will be increased by small increments of 3%. The test will continue to the point at which you cannot go any further. If you feel any fatigue or

discomfort, you may stop the test at any time. An EKG will monitor your heart during the exercise and a physician will be present for safety reasons.

For the MRI scan, you will be asked to lie on a table for about twenty minutes while a machine takes pictures of your stomach and leg.

You will have a special scan of your body called a DEXA scan. You will be asked to lie on a table for about fifteen minutes and the machine will move over your body from head to toe. You will be asked to perform exercise testing, such as lift weights, walk along a track, climb steps to test your muscle strength and find out how well your muscles function. This testing will take about one hour. You will also complete a questionnaire (about the quality of your life) at this visit. The questionnaire will assess how these treatments make you feel. Blood will be taken from your vein (needle puncture into a vein and blood withdrawn) for a number of different blood tests. Approximately 3 tablespoons of blood will be obtained at this visit. A urine sample will be collected at this time.

To find out how this medicine affects the amount of water in your body, you will be asked to drink a small amount of heavy water and a salt solution (sodium bromide). Heavy water is a stable isotope (a non-radioactive compound that is similar to water) which means that it does not produce any radiation and is not harmful to your body. Four 1 ½ tablespoon blood samples will be drawn from a needle in your vein before and over 4 hours after drinking the heavy water and salt solution.

This study is divided into a 2 week screening period and a 12 week treatment period. After the 2 week screening period, all visits are done every 3 weeks. They are summarized as follows:

Visit 1 (Screening): You will be asked to come to a one 30-minute appointment to the Clinical Research Center (CRC) at King/Drew Medical Center. During this appointment, we will conduct the following procedures to find out if you meet all the requirements and if it is safe for you to continue in the study:

- We will ask you about your medical history
- Explain the study and obtain written, informed consent
- We will ask for a blood sample (about 2 tablespoons) for lab tests to find out about your general health
- A complete physical exam and vital signs (blood pressure, heart rate, respirations, and temperature) will be performed
- Chest Xray
- EKG
- You will talk with a dietician who will advise you about what foods to eat
- You will be asked to complete a food record for 3 days in a row before your next visit

If you pass the screening qualifications for visit 1, you will be asked to have an exercise treadmill in our exercise facility at El Camino College. This procedure will last about 20-25

minutes and will be done approximately one week after visit 1. This will complete the screening period. If you pass the treadmill test, you will be asked to return to the CRC for visit 2.

Visit 2: You will be asked to return to the CRC for a total of 4 hours to have tests and blood taken from your vein (needle puncture into a vein and blood withdrawn) for blood tests. The amount of water in your body will be measured by having you drink heavy water and salt solution (sodium bromide) and taking 4 blood samples, each of which is 1.5 teaspoons.

Also, during this visit the following will be done:

- DEXA scan of your body will be done to measure the fat and muscles in your body.
- MRI scan of your stomach and leg to measure the size of your muscles.
- You will be asked to complete a questionnaire (quality of life or QOL) to assess how these treatments make you feel.
- You will be asked to return the completed 3-day food record.
- Dispense experimental medication:
  You will be assigned to one of the three treatments by chance (like tossing of a coin). You will have an equal chance to be in one of the three treatments. You will begin taking one of the experimental medications at visit 2. They are as follows:

1. Oxymetholone, one pill a day and one placebo (inactive pill) pill per day.
2. Oxymetholone, two pills per day.
3. placebo (inactive pill), two pills a day.

After the testing at the CRC, you will be asked to go to El Camino College for Exercise testing. This testing will take about 1 hour. You will be asked to lift weights, walk along a track, climb steps to test your muscle strength and find out how well your muscles function.

Visit 3: You will be asked to return to the CRC for a 30 minute visit. This visit includes:

- Medical history, Vital signs, and check for any illnesses or adverse events (AEs)
- Blood (about 1 teaspoon) for liver tests
- Assess medication compliance and pill count

Visit 4: You will be asked to return to the CRC for a 45 minute visit and to visit El Camino College for a 1 hour exercise testing. The CRC visit includes:

- Medical history and check for any illnesses or adverse events (AEs)
- Assess medication compliance and pill count
- Blood (about 2 teaspoons) for lab tests
- Quality of Life Questionnaire
- Dispense 3-day food record

Visit 5: You will be asked to return to the CRC for a 30 minute visit. This visit will be exactly like visit 3.

Visit 6: You will be asked to return to CRC for a 4 hour visit. You will also be asked to return to El Camino College for a 1 ½ hour visit for an Exercise treadmill and exercise testing. The CRC visit is the same as visit 2.

- **Potential Risks and Discomforts**

The research has several risks and side effects may occur during your participation in the study.

The common side effects of oxymetholone include swelling, weight gain, hypertension, lipid abnormalities, acne, oiliness of skin, breast tenderness and enlargement, and increase in red blood cell count. At the level of medication that is taken by subjects in this study, it is not common to see liver problems, but there is a possibility, such as blood backing up in the liver, yellow jaundice due to bile (a yellow-greenish fluid formed by the liver) backing up in the liver, and abnormal liver tests. The long-term effects of oxymetholone on the prostate are not known.

There is minimal risk involved in obtaining a chest x-ray, since the amount of radiation received is very small. The amount of radiation you will receive from a chest xray is only a small fraction of the amount that each radiation worker is allowed to receive.

It is possible the treadmill test could cause irregularities of the heart beat (e.g., increased heart rate), chest pain or heart attack, and/or shortness of breath. Every effort will be made to minimize these risks. A medical doctor will be present during the treadmill testing. You will be evaluated for evidence of heart disease with a complete history and physical examination, EKG, and chest x-ray prior to undergoing the treadmill test. If any abnormalities are detected that would put you at risk during the treadmill test, you will not be allowed to do the treadmill test or to participate in the study. During the test, if you should experience any symptoms or if your heart activity shows abnormalities, the test will be immediately stopped.

There is minimal risk involved in obtaining a DEXA scan. The estimated radiation dose from a DEXA scan to the whole body is less than 25 millirads (mrads). A millirad is a unit of measurement for radiation. No amount of radiation is considered completely safe. The amount of radiation is relatively less than a chest xray or a dental exam.

The MRI scan poses no risk to most people. However, some people may feel uncomfortable or even claustrophobic (afraid of closed spaces) while lying in the machine. Also, you may hear a banging noise which is caused by the MRI machine. If this occurs and is bothersome to you, earplugs will be available for your use. Individuals with metal fragments or implantable devices, who are at risk from MRI scans, will not undergo this procedure. You will notify the investigators or the person performing the MRI scan if you have a metal fragment in your body or if you use an implantable device such as a pacemaker. In that case, the MRI scan will not be performed.

There are no risks associated with drinking heavy water or sodium bromide salt solution.

The risks of muscle function testing include the possibility of injury and muscle soreness. The risk will be decreased by careful supervision during the testing procedures.

Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site of venipuncture or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Collecting urine samples at various times during the research study may be inconvenient for you.

You may find the questions about your quality of life very personal and some questions some what embarrassing. If you feel uncomfortable answering any questions, you may decline to answer those questions.

Other unpredictable side effects besides those listed above may occur. It is important that you report any drug side effects to your research study doctor. Long-term (years) side effects are not known at this time.

- **ANTICIPATED BENEFITS TO SUBJECTS**

If you participate in the study, you will receive free medical and physical assessments.

- **ANTICIPATED BENEFITS TO SOCIETY**

The information gained from this study **may** help design better treatments for muscle loss in elderly men.

- **ALTERNATIVES TO PARTICIPATION**

There is no alternative therapy currently approved for the treatment of loss of muscle mass in older men.

- **PAYMENT FOR PARTICIPATION**

You will be paid $400.00 ($67.00 per required study visit) if you complete your participation in the study. If you do not complete the study (such as withdrawal from the study by the investigator or your own decision to withdraw), you will be paid for the parts that you do complete. The purpose of these payments is to compensate you for transportation costs, your time, and any inconvenience caused by your participation in the study.

- **FINANCIAL OBLIGATION**

Neither you nor your insurance company will be billed for your participation in this research.

- **EMERGENCY CARE AND COMPENSATION FOR INJURY**

You participate in this research at your own risk. King/Drew Medical Center has not set aside funds for compensation or payment of research related injuries. You are not waiving any legal claims, rights or remedies because of your participation in this research study.

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one Dr. Shalender Bhasin and/or Dr. Singh at (323) 563-9353. If you cannot reach the investigators, you may call the 24 hour number at the hospital emergency department (adult), 310-222-3624.

Date of Revision: 11/7/00
IRB#: 00-05-030-00
Expiration Date: OCT 10 '01

- **PRIVACY AND CONFIDENTIALITY**

Any personal information, research data, and related records for this study will be coded and stored in a locked filing cabinet to prevent access by unauthorized personnel. The only people who will know you are a research subject are members of the research team and, if appropriate your physicians and nurses will know that you are a research subject. Authorized representatives of the Food and Drug Administration (FDA), National Institutes of Health (NIH), the manufacturer of the drug (Oxymetholone), or the funding agency (Unimed), may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

No information about you, or provided by you during the research, will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- if required by law (i.e., child abuse, elder abuse).

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. All data and stored blood, tissue and urine samples will be coded so that only the researchers gathering the original data will be able to link your name and information that identifies you with the coded data/samples. The blood, tissue and urine samples will be stored in Dr. Bhasin's lab at CDU for a period of 5 years and the data will be stored with Dr. Bhasin indefinitely.

All tissue and/or fluid samples are important to this research study. Your samples will be owned by the Drew University or by a third party designated by the University (such as another university or a private company). If a commercial product is developed from this research project, Drew University or its designee will own the commercial product. You will not profit financially from such a product.

- **PARTICIPATION AND WITHDRAWAL**

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with CDU, or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at CDU.

If you are a CDU student, you may choose not to participate or to stop your participation at any time. This will not affect your grades or class standing at CDU. You will not be offered or receive any special consideration if you participate in this research.

Date of Revision: 11/7/00
IRB#: 00-05-030-00
Expiration Date: OCT 10 '01

IRB COMMITTEE APPROVED
DATE OCT 11 2000
VOID AFTER OCT 10 2001

If you are a CDU employee, your participation in this research is in no way part of your university duties, and your refusal to participate will not in any way affect your employment with the university, or the benefits, privileges, or opportunities associated with your employment. You will not be offered or receive any special consideration if you participate in research.

WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience side effects or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, Dr. Bhasin, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

If you must drop out because the investigator asks you to (rather than because you have decided on your own to withdraw), you will be paid as if you had fully participated in and completed the trial.

- **NEW FINDINGS**

During the course of the study, you will be informed of any significant new findings (either good or bad) that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

- **IDENTIFICATION OF INVESTIGATORS**

If you have any questions about the research, please feel free to contact Dr. Shalender Bhasin, and/or Dr. Singh at (323) 563-9353.

- **RIGHTS OF RESEARCH SUBJECTS**

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research subject, you may contact the Drew University Office for Protection of Human Subjects at 323-563-5902.

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) and understand the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

_____
Name of Subject

_____
Name of Legal Representative *(if not applicable, delete signature lines and references to legal representation)*

_____ _____
Signature of Subject or Legal Representative Date

All blood samples are important to this research study. Your sample will be owned by the Drew University or by a third party designated by the University (such as another University or a private company) and may be used for other studies. If a commercial product is developed from this research project, Drew University or its designee will own the commercial product. You will not profit financially from such a product.

Please check the appropriate box below and initial:

☐ _____I agree to have my tissue/fluid sample shared with other researchers.

☐ _____ I do not want my tissue/fluid sample shared with other researchers.

INFORMATION ABOUT YOUR SAMPLE

Please indicate by checking and initialing the category below what type of information you want to receive. It is your responsibility to let the investigator know if your address and/or telephone number changes. The contact information is in this informed consent form under "Identification of Investigators".

☐ _____General Information about what the study found

☐ _____Specific Information about what the study found about me

☐ _____I do not want any information about my sample

Date of Revision: 11/7/00
IRB#: 00-05-030-00
Expiration Date: OCT to 01

IRB COMMITTEE APPROVED
DATE OCT 11 2000
VOID AFTER 10 2001

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject or his/her legal representative, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____
Name of Investigator

_____ _____
Signature of Investigator Date (must be the same date as subject's)

SIGNATURE OF WITNESS *(If required by the Drew IRB)*

My signature as witness certified that the subject or his/her legal representative signed this consent form in my presence as his/her voluntary act and deed.

_____
Name of Witness

_____ _____
Signature of Witness Date (must be the same date as subject's)

Date of Revision: 11/7/00
IRB#: 00-05-030-00
Expiration Date: OCT 10 '01

#30

CHARLES R. DREW
UNIVERSITY OF MEDICINE & SCIENCE

vision of Endocrinology,
etabolism and Molecular Medicine

July 12, 2000

To: Carrie Fisher, Ph.D.
Institutional Review Board

From: Shalender Bhasin, M.D.

Re: Protocol, "Dose Ranging Study of Oxymetholone in Frail Elderly Men: A Phase II Proof
of Concept Study" (A double-blind study)

This letter is to inform the IRB of a Post-study Adverse Event which occurred to one of the subjects [redacted], from the collaborating site at LA-USC Medical Center. Please see the attached memorandum and notes from LA-USC.

If you have any further questions, you may contact me at 323.563.9353.

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California 90059 Telephone: (323)563-9353 Fax: (323)563-9352

Allegation 1. The intervention described in the above-referenced publication poses the risk of hypogonadism and the intervention itself introduces a confounding variable into the study design.

Response:

The study intervention that was evaluated in the referenced article (Am J Physiol Endocrinol Metab 2003; 284:E120-128) did not cause hypogonadism (symptoms of low testosterone and/or decreases in serum levels of the male hormone, testosterone). To the contrary, lean body tissue (which includes muscle mass) and voluntary skeletal muscle strength improved significantly by the end of study therapy, reflecting improvements in overall androgen status (Bhasin 2001). Moreover, serum luteinizing hormone (LH) was significantly decreased by –6.0±4.1 IU/L and –5.6±9.7 IU/L with the 50 and 100 mg/day doses, respectively, reflecting a state of increased androgen hormone status. We will also present data from a parallel study that investigated the durability of androgen effects in older, community dwelling men at risk for decreased muscle mass (sarcopenia) and frailty, in which serum testosterone levels were identical prior to pretreatment and 12 weeks after stopping study therapy, indicating that post-treatment hypogonadism did not occur. Finally, we will review why there was no a priori reason to expect that the study interventions would cause hypogonadism.

To begin, there has been considerable debate and controversy about the issue of whether the androgenic and anabolic properties of any androgen, whether testosterone or semi-synthetic derivative of testosterone, can be dissociated. Many endocrinologists believe, based on emerging data, that the anabolic and androgenic effects of these agents are mediated through the same nuclear androgen receptor and that these properties cannot

Allegation # 5. ***"Research plan did not make adequate provision for monitoring the data collected to ensure the safety of subjects. It is claimed that serum testosterone levels can not be accurately measured in men treated with oxymetholone and failure to do this constitutes potentially the "most serious and flagrant disregard for the protection of human subjects."***

Response:

The OHRP letter claims that serum testosterone levels can be measured accurately in the sera of men treated with oxymetholone. This assertion is based on simplistic assumptions and does not recognize the many difficulties that confound measurements of circulating testosterone concentrations in subjects treated with androgens. Dr. Bhasin's laboratory went to great lengths to develop and validate accurate methods for the measurement of serum testosterone levels in men treated with androgens such as oxymetholone and oxandrolone. However, as described below, for a variety of complex methodological and logistical reasons, these efforts did not come to fruition.

The OHRP letter includes tables from the manufacturer of the assay reagent and claims that the cross-reactivity of oxymetholone in testosterone assay is relatively small (1-2%). We investigated the cross-reactivity of oxymetholone in Dr. Bhasin's laboratory and verified that the cross-reactivity was indeed relatively small. However, the assertion that just because the cross-reactivity of oxymetholone in testosterone assay is small, it is not a problem reflects naiveté about radioimmunoassays, because it ignores several other complex issues that frustrated our efforts to develop an accurate measurement system:

a. We did not know (and still do not know) what the circulating concentrations of oxymetholone are after administration of 50 and 100 mg of this drug. While the percent cross-reactivity of oxymetholone in testosterone assay might appear to be small, if the circulating concentrations of oxymetholone are in 10,000 ng/dL range, as we suspect they might be, they could contribute very substantially to the measured testosterone immuno-reactivity. We do not have an assay for the measurement of serum oxymetholone concentrations, and therefore, it was not possible to determine the exact contribution of oxymetholone cross-reactivity to the measured testosterone concentrations.

b. A more difficult issue that we faced was that the metabolism of oxymetholone in humans had not been studied in detail, and we did not know whether and how much the various metabolites of oxymetholone cross-react in testosterone assay or whether these metabolites are biologically active.

c. Importantly, we did measure serum testosterone levels in four men treated with oxymetholone at baseline and after 6 and 12 weeks of treatment. In these subjects, serum testosterone levels did not show a significant change from baseline.

	Baseline	**Week 6**	**Week 12**
Mean±SEM Serum Testosterone (ng/dL)	457±65	370±40	370±131

Table 2. Mean serum testosterone concentrations by a direct radio-immunoassay in four older men at baseline and after 6 and 12 weeks of treatment with 100 mg/day oxymetholone.

This study was designed to answer some of the issues left unresolved by previous clinical trials.

Previous studies of testosterone administration in older men had demonstrated modest gains in fat-free mass (e.g., Snyder et al, 1999; Kenny et al, 2001; Tenover et al, 1992; Tenover, 2000; Ferrando et al, 2003; Urban et al, 1995; Marin et al, 1992; Marin et al, 1995; Sih et al, 1997; Morley et al, 1993). However, these initial studies of testosterone supplementation failed to demonstrate significant gains in muscle strength. After careful review of this literature and after considerable discussion with the investigators involved in these earlier studies, investigators concluded that the methods used for measurements of muscle performance in previous studies were significantly flawed and confounded by learning effect and ceiling and floor effects.

The issue of whether androgen administration improves muscle strength has important implications; if androgen administration does not improve muscle performance, then there is little clinical utility in administering androgens to older men or men with chronic illness. In this feasibility study, the investigators wanted to use more rigorous and validated measures of muscle performance, which they had previously shown to be androgen responsive in healthy, hypogonadal men (Bhasin et al, 1997), and in HIV-infected men with low testosterone levels (Bhasin et al, 2000). The investigators determined that the use of an oral androgen would be more acceptable by older men than an injectable androgen in terms of convenience and subject compliance.

Allegation 4: Failure to ensure that the research plan makes adequate provision for monitoring the data collected to ensure safety of subjects, as required by HHS regulations at 45 CFR 46.111(a)(6). In specific, it is alleged that the research failed to evaluate testosterone levels at the end of the study to monitor for hypogonadism.

Drew's Endocrinology laboratory went to great lengths to develop and validate accurate methods for the measurement of serum testosterone levels in men treated with androgens such as oxymetholone and oxandrolone. As an exploratory exercise, the Investigator measured serum testosterone levels in three men treated with oxymetholone at baseline and after 6 and 12 weeks of treatment. In these subjects, serum testosterone levels did not show a significant change from baseline.

	Baseline	**Week 6**	**Week 12**
Mean±SEM Serum Testosterone (ng/dL)	457±65	370±40	370±131

Table 1. Mean serum testosterone concentrations by a direct radio-immunoassay in three older men at baseline and after 6 and 12 weeks of treatment with 100 mg/day oxymetholone.

However, serum LH concentrations were suppressed modestly; this led us to suspect that either oxymetholone or one of its metabolites was cross-reacting in testosterone assay. Because we were not able to resolve the issue of cross-reactivity with any degree of certainty, we could not assure the accuracy of the testosterone measurements. It was because of this uncertainty that we opted not to report the data on testosterone levels in our manuscript. Thus, the claim that testosterone can be measured accurately in men treated with oxymetholone reflects an unawareness of these complex issues of cross-reactivity.

Allegation 5: The informed consent process for the research failed to include the elements required by HHS regulations at 45 CFR 46.116. In specific, it is alleged that since the research did not take in to account the possibility of the development of hypogonadism, the informed consent process failed.

Drew's IRB reviewed this research study for the first time at their regularly convened meeting on September 13, 2000. A physician, Dr. Goldman, led the discussion regarding concerns of subjects receiving androgens. The IRB accessed the risk to the subjects. The IRB reviewed the informed consent document. The informed consent document prepared by the Investigator is substantially similar to the Drew informed consent template posted on the Drew website in 2000. Informed Consent template suggest a narrative in simple language for the subject regarding the following headings,

'Background/Purpose of the Study',
'Procedures',
'Potential Risks and Discomforts,'
Anticipated Benefits to Subjects,'
'Anticipated Benefits to Society,'
'Alternatives to Participation,'
'Payment for Participation,'
'Financial Obligation,'
'Emergency Care and Compensation for Injury,'
'Privacy and Confidentiality'
'Participation and Withdrawal'
'Withdrawal of Participation By the Investigator'
'New Findings'
'Identification of Investigators'
'Rights of Research Subjects'

The IRB voted to defer the study and requested several modifications to be made to the application and the informed consent document prior to resubmission of the research study to the IRB review. [See Appendix for Minutes]

The modified application and informed consent documents were reviewed at the regular, convened meeting of the IRB on October 11, 2000. The IRB discussed all aspects of the modified research study application and informed consent

The modified application and informed consent documents were reviewed at the regular, convened meeting of the IRB on October 11, 2000. The IRB discussed all aspects of the modified research study application and informed consent documents. It was determined that the research study was acceptable in regard to subject participation and research design. The study was approved for 12 months. [See Appendix for Minutes]

Drew does not agree that the IRB failed to appreciate risks of hypogonadism to the subjects. The informed consent document appropriately listed known risks of use of androgens. The investigator made each modification requested by the IRB at the September 2000 meeting. The Investigator offered an explanation of safeguards to subjects in his letter to the IRB, dated November 8, 2000, regarding the risk of subjects for elevated liver enzymes.

"The liver enzymes fluctuate in healthy elderly men from week to week, and mild elevations in AL and AST may be found in men without active liver disease. It is customary in clinical trials of androgenic steroids to set the inclusion threshold at 3 times the upper limit of normal, and not 2.5 times the upper limit of normal. In any event, we will closely monitor liver enzymes through the study in all participants. This strategy has worked well in our previous androgen studies and has been acceptable to Federal Agencies."

In summary, the overall allegations of noncompliance of the HHS regulations at 45 CFR 46 are without merit. Specifically, 1) men treated with oxymetholone or 2) men being treated with an anabolic androgen are androgen-deficient are at risk of development of hypogonadism is not supported by data or medical literature in 2000 or even currently. The research was conducted as a collaborative study at University Southern California (USC) and Charles R. Drew University. The study was reviewed and approved by both the USC and Drew IRB in accordance with federal regulations.

If you require any further documentation or references, please contact Ms. Nancy Moody, Director, Office for Protection of Human Subjects at 323 563 4906.

Sincerely,

Charles K Francis MD

Charles K. Francis, M.D.
President

August 21, 2003

VIA OVERNIGHT MAIL

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

RE: Human Research Subject Protection Under Multiple Project Assurance (MPA) M-1299

Research Publication: E. Schroeder et al., Effects of an Oral Androgen on Muscle and Metabolism in Older, Community-Dwelling Men, *Am. J. Physiol. Endocrinol. Metab.* 284: E120-E128, 2003.

Dear Dr. McNeilly:

The University of Southern California (USC) has received your letter dated July 9, 2003 concerning allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects involving the above-referenced research publication. Provost Lloyd Armstrong has asked that I respond on behalf of USC, since I am the Chair of the Health Sciences Campus Institutional Review Board (HSC IRB), which reviewed and approved the study referenced above.

We have conducted a thorough investigation of the allegations related to this research project and have concluded that the project was conducted in accordance with HHS regulations regarding the protection of human subjects in research. Specific responses to the first five (5) allegations in your July 9 letter are set forth below. In addition, we enclose the complete IRB file for this research study, per your request.

Allegation 1. Failure to conduct the above-referenced research using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by HHS regulations at 45 CFR 46.111(a)(1). In specific, the complaint alleges that the intervention described in the above-referenced publication poses the risk of hypogonadism and the intervention itself introduces a confounding variable into the study design.

Response:

Our review has determined that the above-referenced research was conducted using procedures that are consistent with sound research design and did not unnecessarily expose subjects to risk of hypogonadism.

To put this allegation into context, it is important to understand the purpose of the study. The research project was designed to determine whether an oral androgen supplement increased muscle mass and strength in relatively healthy, older men (ages 65- 80 years of age) who were at risk for sarcopenia (i.e., decreased muscle mass and frailty).

Health Sciences Institutional Review Board
IRD Building, Room 425
2020 Zonal Avenue
Los Angeles, CA 90033
Tel: 323-223-2340
Fax: 323-224-8389

Androgens, the male hormone testosterone and structurally similar drugs that produce changes in body muscle gain and fat and secondary sexual characteristics (hair and beard growth, penile growth) typical of men. Testosterone is one of the most important types of androgens in men.

The study subjects were given an oral androgen supplement, oxymetholone, which is a generic form of Anadrol. Oxymetholone is a Class II steroid hormone with similar properties to male testosterone. Subjects were given oxymetholone for a duration of 12 weeks at levels well below the FDA approved dosage. The subjects were given complete physicals at prior to treatment, study week six and study week twelve.

The study findings supported the researchers' hypothesis, specifically, that the administration of the androgen supplement increased muscle mass and strength and decreased fat mass in the study subjects while they received the supplement. In addition, lutenizing hormone (LH) concentration levels decreased in study subjects indicating that the supplement was supplying additional androgen levels and there was no hypogonadism.

The allegation relates to the risk of hypogonadism, or reduction in testosterone production, which results if the gonad does not produce the amount of sex steroid sufficient to suppress secretion of the LH at normal levels. The symptoms of hypogonadism include fatigue, loss of muscle mass, muscle strength, decreased sexual drive, and increase in body fat which are associated with increases in the amount of LH in blood.

The allegation that the study is not based on sound research design suggests a basic misunderstanding of the science that supports the protocol. First, hypogonadism was not a risk while the study was in progress because the subjects received an androgen supplement. While oxymetholone could suppress internal testosterone production, the externally administered androgen supplement should, and did, maintain androgen levels. In other words, hypogonadism would occur if androgen activity was reduced , but in this study, androgen activity was maintained (if not enhanced) via external administration of an androgen supplement. As a result, the study subjects did not experience any hypogonadal symptoms during the term of the study. To the contrary, the improvement in muscle and fat mass and decrease in pituitary LH levels indicates that the study subjects had increased androgen activity, as expected.

Second, as described below in response to Allegation #2, there was no reason to believe that hypogonadism would occur at the end of the 12-week study period, after androgen cessation. Nor would the occurrence of hypogonadism be clinically significant such as to compromise study design or affect IRB approval of the study.

Accordingly, we believe that the study design was sound and did not expose subjects to unnecessary risk of hypogonadism.

The complaint also alleges that, " . . . the intervention itself introduces a confounding variable into the study." This allegation is not particularly clear, but confounding bias was not possible since regulation of testicular production (through the pituitary, hypothalamus and testicles) was not disrupted and responded in a physiologic manner to the androgen treatment.

Allegation # 2. ***"Failure to ensure that the risks to the subjects are reasonable in relation to the anticipated benefits, as required by HHS regulations at 45 CFR 46.111(a)(2). In specific it is alleged that it is not possible to accurately determine the extent of hypogonadism and that each subject will suffer after androgen cessation."***

Response:

The investigators and the HSC IRB complied with federal regulations by ensuring that risks of hypogonadism to subjects after androgen cessation were reasonable in relation to anticipated benefits. As described in further detail below:

- No similar studies that had been previously conducted reported any evidence of hypogonadism after androgen cessation, nor were investigators required to investigate if hypogonadism occurred

- There is no evidence to suggest that normal testicular functions did not recover quickly in subjects and unpublished data from the above referenced study supports this assertion

- The investigators who conducted the above referenced study also performed a subsequent study, which demonstrated that testosterone levels did return to normal function quickly

First, it is important to remember that a number of prior studies have been conducted involving the administration of androgen supplements in males. There is no evidence from any prior research to suggest that androgen cessation resulted in a risk of hypogonadism.[1] Nor are we aware of any researchers who were required to follow subjects after treatment cessation. It should be noted that previous studies conducted by World Health Organization have demonstrated complete recovery of the hypothalamic-pituitary-testicular axis after administration of supraphysiologic doses of testosterone for a year (WHO Male Task Force 1990).

Further, there is no evidence, either in the above referenced study or any adverse events reported from prior research to suggest that normal testicular function would not recover quickly after cessation of the androgen supplement. That is particularly true in the above referenced study, which was of short duration and involved androgen doses well below the FDA approved dosage. Indeed, even the Physicians' Desk Reference (PDR) does not list hypogonadism as a possible risk of androgen cessation after treatment with oxymetholone.

By analogy, in studies of contraception in young healthy women with normal menstrual cycles who are given synthetic estrogens for birth control, investigators were not required to inform study subjects that this treatment will cause estrogen deficiency. However, the birth control pill will predictably suppress the woman's natural internal production of estradiol. This is not a clinical situation of "estrogen deficiency," because the estrogen in the birth control pill is making up for the loss of endogenous estrogen production. Investigators were not required to give estradiol replacement to women treated with birth control pills despite knowledge that the exogenously administered, synthetic estrogen in birth control pill will suppress production of the endogenous estradiol. Thus, we believe that this scenario is identical to studies investigating treatment with androgens in men, especially when the doses are within the labeling guidelines and the treatment is of a short duration and it is anticipated that the studies therapy will improve androgenic activity and health benefits, such as in this case.

Importantly, the investigators in the above referenced study did measure serum testosterone levels in four men treated with oxymetholone at baseline and after 6 and 12 weeks of treatment. In these subjects, serum testosterone levels did not show a significant change from baseline.[2] However, because the investigators could not resolve the issue of cross-

[1] Previous studies that used oxandrolone, a synthetic androgen with similar anabolic activity, reported no change in serum testosterone levels during oxandrolone administration (Sheffield-Moore et al, 1999) None of the previous studies involving androgen administration in older men (Snyder et al, 1999; Tenover 2000; Tenover 1992; Morley et al, 1993; Sih et al, 1997; Kenny et al, 2001; Marin et al, 1992; Marin et al, 1995) or men with chronic illness (Grinspoon et al, 1998; Hengge et al, 2003; Strawford et al, 1999; Schols et al, 1995; Hurtado et al, 1993), or funded by NIH or pharmaceutical companies, have followed subjects after treatment discontinuation.

2

	Baseline	**Week 6**	**Week 12**
Mean±SEM Serum Testosterone (ng/dL)	457±65	370±40	370±131

Table 1. Mean serum testosterone concentrations by a direct radio-immunoassay in four older men at baseline and after 6 and 12 weeks of treatment with 100 mg/day oxymetholone.

reactivity with any degree of certainty and therefore could not assure the accuracy of the testosterone measurements, they did not report the data on testosterone levels in the above manuscript.

Finally, the investigators subsequently conducted a follow-up study using oxandrolone (oral androgen similar to oxymetholone) at the licensed dose for weight loss (20mg/day) for 12 weeks in older men (60-90 years of age) at risk for sarcopenia and frailty. The purpose of the second study was to assess the durability of effects of treatment on measures of skeletal muscle strength and body composition 12 weeks after discontinuing oxandrolone (ie, at study week 24). The table below shows that testosterone levels 12 weeks after discontinuing study therapy were similar to baseline in both the oxandrolone and placebo groups.

Testosterone ng/dL	Baseline	Study Week 24	P values
Oxandrolone (n=20)	369±147 ng/dL	358±119 ng/dL	0.28
Placebo (n=12)	357±153 ng/dL	421±196 ng/dL	0.26

Table 2. Testosterone levels at baseline and 12 weeks after completion of study therapy (i.e., study week 24) in older men randomized in a 2:1 manner to receive oxandrolone at the licensed dose or matching placebo for 12 weeks.

These data confirm that oxandrolone did not produce hypogonadism after treatment was discontinued.

With that said, the allegations raise an interesting research question from a scientific point of view since we are not aware that the recovery period after androgen cessation has ever been specifically studied. However, the results of such research, if it ever were determined to be sufficiently significant for clinical study, would not have impacted the design of this study nor the informed consent process for study subjects.

Allegation # 3. ***"Failure to ensure that the selection of subjects is equitable as required by HHS regulations at 45 CFR 46.111(a)(3). In specific it is alleged that the investigators failed to account for the possibility of hypogonadism and that the research should have been conducted on a non-elderly population."***

Response:

We believe that the selection of study participants was consistent with the requirements 45 CFR 46.111(a)(3) and the ethical principles set forth in the Belmont Report.

Although a number of previous studies had verified that testosterone supplementation in healthy, young men increases muscle size and strength, the effects of testosterone administration on mass and performance in older men had been inconsistent. Accordingly, it was this population of males that were the subjects of the study.

As indicated above, sarcopenia and frailty with a number of attendant medical complications that portend a high risk for disability, morbidity, and mortality are a frequent concomitant of aging in men. Several studies have shown that the loss of muscle mass and strength with aging is associated with declines in bioavailable testosterone in older men (Baumgartner et al, 1998; Melton et al, 2000; Roy et al, 2002). The subjects treated in the study at USC were at risk for sarcopenia and frailty based on age, but were community dwelling, relatively healthy older men with levels of testosterone that were lower than those of men two-to-three decades younger. Because these older subjects are the population at risk for sarcopenia and frailty but were not by definition institutionalized and vulnerable, they were the appropriate test population.

The selection of study subjects was equitable. The clinical problems of age-related sarcopenia that this study was designed to address could not be answered by conducting a study in young men who have higher levels of

testosterone, muscle mass, and strength; the selection of the study population was dictated by the available data on the epidemiology of sarcopenia . Thus, we disagree that the selection of subjects was not equitable and these were a vulnerable population.

Allegation # 4. ***"Failure to ensure that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, as required by HHS regulations at 45 CFR 46.111(a)(6). In specific, it is alleged that the research failed to evaluate testosterone levels at the end of the study to monitor for hypogonadism."***

Response:

As discussed above, hypogonadism did not occur during or after androgen therapy in older men in the research study at issue. To the contrary, there were improvements in androgen sensitive tissues (namely skeletal muscle mass and adipose tissue), study subjects did not complain of symptoms of androgen deficiency (i.e., hypogonadism) during or at the completion of study therapy, and LH levels declined indicating increased androgen activity. Again, if androgen deficiency or hypogonadism had occurred as a result of study therapy, LH levels would have increased. Moreover, there was not evidence in the scientific literature or provided by the manufacturer or listed in the PDR to suggest that hypogonadism is a risk of this study therapy. Also, as we have stated, the US Food and Drug Administration and other IRBs have not required follow up of subjects treated with this or other anabolic-androgenic agents, such as oxandrolone and nandrolone in clinical research studies. However, as set forth above, a study involving treatment with a very similar anabolic-androgen, namely, oxandrolone, did not cause a state of hypogonadism in a similar population of older men at risk for sarcopenia and frailty.

For these reasons, we believe that there is no merit to this allegation as it assumes that hypogonadism is a risk and that it is clinically significant to the design of the study that it requires monitoring – a premise that has no basis.

Allegation # 5. ***"The informed consent process for the research failed to include the elements required by HHS regulations at 45 CFR 46.116. In specific, it is alleged that since the research did not take into account the possibility of the development of hypogonadism, the informed consent process failed to include the following:***

> ***(a) A description of the reasonably foreseeable risks or discomforts to the subject.***
>
> ***(b) An explanation as to whether any medical treatments are available if injury occurs.***
>
> ***(c) A statement that significant new findings developed in the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.***
>
> ***(d) The consequences of a subject's decision to withdraw from the research.***
>
> ***(e) The expected duration of the subject's participation in the research.***
>
> ***(f) Any additional costs to the subject that may result from participation in the research.***

Response:

This is simply incorrect. The informed consent document used in this research study does list a number of possible risks related to administration of an androgen supplement, including certain symptoms that are associated with hypogonadism. Hypogonadism is not referenced by name because that is a medical term and the HSC IRB does not permit the use of medical terminology without explanatory lay language.

Symptoms that would occur with hypogonadism as well as other symptoms are clearly referenced in the informed consent.

Again, it should be noted that none of the subjects reported experiencing any of these symptoms.

I trust that this responds to your letter. Please do not hesitate to contact me directly if you have any further questions.

Sincerely,

Darcy V. Spicer, MD
Chair, Health Sciences Campus Institutional Review Board

Enclosures: Copy of IRB file

cc (without enclosures): Lloyd Armstrong, Provost and Senior Vice President
Cornelius W. Sullivan, Vice Provost for Research
J. Van Der Meulen, Vice President, Health Affairs
Stephen J. Ryan, Dean, Keck School of Medicine
Laura L. LaCorte, Senior Associate Vice President, Compliance
Ronald Kauffman, Associate Dean for Administration
Fred Sattler, MD
Dr. David Lepay, FDA

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INVESTIGATOR INITIATED DOSE RANGING STUDY OF OXYMETHOLONE IN FRAIL ELDERLY MEN: A Phase I/II Proof of Concept Study

Departments of Medicine, Biokinesiology and Physical Therapy, and Radiology

Investigators: Fred Sattler, M.D.
Victoria Jaque, PhD
Michael Terk, MD

Version 2.0

24 hour telephone number: (323) 343-8288

The University of Southern California invites you to participate in a research study of oxymetholone (Anadrol) for treatment of frailty in elderly men. The nature of the study will be explained to you. Please read this form and ask any questions that come to mind.

INFORMED CONSENT: You are being asked to take part in the research study named above because of you are 65-75 years of age which puts you at risk for frailty due to the loss of muscle. This is a clinical study of a marketed drug, oxymetholone (Anadrol), which is FDA-approved for other conditions including anemia due to impaired production of red cells by the bone marrow. Oxymetholone has not previously been tested in elderly men at risk for frailty. Before you can decide whether or not to take part in this study, we would like to explain the purpose of the study, how it may help you, any risks to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY: This consent form gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is entirely voluntary;
- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your routine medical care

PURPOSE: The purpose of this 12-week treatment study is to determine the possible effectiveness and safety of a medication, called oxymetholone (Anadrol). This study will try to determine if oxymetholone treatment can increase one's ability to gain muscle tissue which is necessary for strength and activities of daily living such as stair climbing, arising from a chair, walking with balance, sense of well being and independent living.

Approximately 30 subjects will be randomized (assigned by chance) to three study treatment groups with approximately 10 subjects per group.

BACKGROUND: From the age of 20 to 90 years of age, persons progressively lose muscle mass such that by 90 years the average person has about ½ the muscle mass that they had in their 20s. This loss of muscle is also associated with a loss of strength and physical activity. Thus, with aging there is often progressive weakness and there may be difficulty with activities such as arising from a chair, climbing stairs, maintaining a rapid walking pace, progressive loss of balance, etc. The male hormone testosterone is the most important regulator the body has to maintain muscle mass and strength that are necessary for activities of daily living and living independently. With aging, there is a loss of testosterone. By the age of 65 years, up to 80% of men will have levels of testosterone that are significantly lower than for younger men. However, despite being lower, these blood levels of testosterone will in most cases still be in the normal range and sufficient to maintain sexual function.

Studies have shown that in young men with very low levels of testosterone in the blood (a disorder called hypogonadism) giving extra testosterone by frequent injections (usually every two weeks) increases muscle mass and strength. What is unknown is whether giving testosterone or one of its derivatives (known as anabolic steroids) will increase muscle mass and strength in elderly men who have blood levels of testosterone that are lower than for normal men who are younger. In recent, carefully done studies, in which men have been treated with either testosterone or anabolic agents, total body fat also decreased and as a consequence there were actually improvements in blood lipids (various types of fats such as cholesterol). Most of the fat lost was in the abdomen. This is important since excess amounts of intra-abdominal fat in men is a risk factor for developing diabetes and serious complications resulting from hardening of the arteries such as heart attack and stroke. If the effects of such therapy were sustained, this might result in decreased the risk of developing diabetes or vascular problems such as stroke or heart attack.

The anabolic steroid to be tested in this study is oxymetholone (Anadrol) which is licensed by the United States Food and Drug Administration for treatment of anemia and has been tested for other illnesses. Unlike testosterone, Anadrol can be taken by mouth. In AIDS patients, a recent report indicated that treatment with 150 mg of Anadrol daily resulted in significant increases in body weight and was well tolerated without serious effects after 6-12 months of therapy. Thus, the goal of this study is to determine if Anadrol will increase muscle mass, strength, and performance of important activities of daily living in elderly men who are increased risk of frailty. A second important objective is to determine how well this treatment is tolerated in persons more than 65 years of age. The dose of Anadrol to be tested in this study is either 50 or 100 mg per day.

PROCEDURES: If you decide to enroll in this study and sign this consent form, you will be evaluated to be sure that you qualify for the study. Before the study treatment is started, your medical history will be taken and you will have a complete physical examination including a rectal so that your prostate can be examined. You will also have a chest X-ray and electrocardiogram (EKG) done to make sure that you do not have active lung or heart disease. In addition, testing will also include having about 30 ml (two tablespoons) of blood drawn from a vein in your arm to determine your blood counts, blood chemistries, testosterone level, and prostatic antigen. Finally, a registered dietician will ask you questions about your diet and will tell you how to fill out a food diary. The diary will be filled out for a 3-day period before the baseline visit and before the 6 and 12 week visits.

If all of the tests indicate that you are eligible for the study, you will be assigned an appointment for your baseline (entry) visits within the following 14 days. You will be asked not to eat or drink anything (except water) after 8:00 PM the evening before your baseline evaluation. At that visit, you will also be asked to complete questionnaires asking about 1) how you view your health status, your sense of well being and satisfaction, your sexual function and desires and 2) your exercise habits. About 30 ml (2 tablespoons) of blood will be drawn for lipids (types of fat) and

hormones. Your weight and body composition (amount of lean tissue and body fat) will also determined by ~~four~~ five different measurements. ~~Three of these tests will be done at the baseline evaluation and the MRI will be scheduled prior to the baseline evaluation.~~

1). Bioelectrical impedance analysis (BIA). You will lie on a flat surface. Electrode pads will be attached to one wrist and one ankle, and then a very weak, electrical current will be briefly passed through your body. You will not feel anything and the test will take less than 5 minutes.

2) Dual energy X-ray absorptiometry (DEXA). You will lie on a flat surface and an X-ray of your entire body will be taken. This will not hurt you and will take approximately 30-40 minutes.

3) Magnetic resonance imaging (MRI). This test uses magnets and not radiation to take pictures of the tissues of your body. You will not be able participate in the study if you have and metal in your body (eg. pace maker, plate in bone) and you may not wear any metal bracelets, watch, etc during the MRI. In this study, one MRI picture of your abdomen, two of your right leg, and one of your right arm will be obtained. The test does not hurt and will take about 30 minutes. Please see the attached informed consent.

4) Anthropometric measurements. The circumference (diameter, distance around) of your abdomen at two levels, your hips, thigh, and upper arm will be measured.

5) Total body and extracellular water. To determine whether the experimental therapy increases the amount of water in your body, you will undergoing two different measurements done simultaneously. These two tests will require about 5 hours. Before the test, you will have a small an intravenous (IV) line (a small plastic tube) inserted in one of the veins in your forearm and a solution of salt and water similar to what is already in your blood will be slowly infused through the IV tubing. Once everything is ready, you will receive a small injection of heavy water (D2O) followed by a small infection of a salt solution (NaBr) through the IV tubing. These are both stable isotopes which means that they do not produce radiation and are not associated with any dangers to your health. Another small IV line will be placed in your other arm for drawing small samples of blood (about 2/3 of a tablespoonful each). These samples will be obtained 15 minutes before, immediately before, and then 2,3 and 4 hours after the D2O and NaBr are injected. After the last tube of blood is drawn, the IV lines will be removed.

You will also visit the exercise laboratory and have a series of tests done to measure your muscle strength and how well you can perform certain activities of daily living such as rising from a chair, your walking speed, ability to climb stairs to 13 feet, etc. You will be given ample opportunity to "warm-up" and will be given full instructions by an exercise specialist about how to do the tests. You will be coached through the tests to make sure that your form is correct. You will be allowed to stop if you experience severe tiredness, chest pain, or any condition that could be harmful to you. The session will take 1 to 1½ hours.

For the 12 week treatment period, you will be randomized (assigned by chance) to receive one of three regimens: each of which will involve taking two tablets every morning. You will receive one of the following:

1) Two placebo tablets (an inactive substance almost identical in appearance to the drug being tested)
2) One tablet with 50 mg of oxymetholone and one placebo tablet
3) Two tablets of 50 mg of oxymetholone

each) will be obtained 15 minutes before, immediately before, and then 2,3 and 4 hours after the D2O and NaBr are swallowed. After the last tube of blood is drawn, the IV line will be removed.

You will also visit the exercise laboratory and have a series of tests done to measure your muscle strength and how well you can perform certain activities of daily living such as rising from a chair, your walking speed, ability to climb stairs (4 steps), etc. You will be given ample opportunity to "warm-up" and will be given full instructions by an exercise specialist about how to do the tests. You will be coached through the tests to make sure that your form is correct. You will be allowed to stop if you experience severe tiredness, chest pain, or any condition that could be harmful to you. The session will take 1 to 1½ hours.

For the 12 week treatment period, you will be randomized (assigned by chance) to receive one of three regimens: each of which will involve taking two tablets every morning. You will receive one of the following:

1) Two placebo tablets (an inactive substance almost identical in appearance to the drug being tested)
2) One tablet with 50 mg of oxymetholone and one placebo tablet
3) Two tablets of 50 mg of oxymetholone

Neither your doctor nor you will know whether or not you are receiving active drug or placebo for the 12 weeks of the study. In the event of a serious adverse event, your study therapy will be immediately discontinued and you will immediately be given appropriate medical care, but you will not be informed of which treatment you were receiving until the study is completed.

Every three weeks for the 12 weeks (at the end of study weeks 3, 6, 9, and 12), you will return to for additional evaluations including history of how well you are tolerating your medications and whether you developed any new symptoms. At week 3 you have a physical examination and 10 ml (2 teaspoons) of blood will be drawn to make sure that you are not having inflammation in your liver. to the liver. At study weeks 6 and 12, the same assessments will be done as at baseline (first day of treatment) but you will not have a chest X-ray or EKG and there will be no MRI or measurements of body water at week 6. Study week 9 will be a limited visit similar to week 3. At the completion of the week 12 evaluation, the study will be completed for you, unless you have experienced a side effect from the treatment and then you will be evaluated periodically until the problem has resolved.

You should talk to your study nurse or doctor before taking any non-study medications or enrolling in other clinical trials. Study drug will not be provided after the 12-week study period.

DISCOMFORTS AND RISKS

Oxymetholone is an anabolic steroid and may cause the following

Acne or oily skin
Bodily hair growth or loss
Depression and tiredness
Difficulty with sleep
Nausea and/or vomiting
Inflammation of the liver
Increased or decreased sex drive
Enlargement or cancer of the prostate
Liver tumors
Abnormal pools of blood in the liver
Abnormal pools of blood in the spleen
Swelling of the legs
Decreased blood clotting
Increased cholesterol
Elevated red blood cell counts

- You have a bad effect to the study treatment;
- The study is canceled by the Food and Drug Administration (FDA) or Unimed (the company supplying study treatment); and/or
- Other administrative reasons.

If you discontinue the study treatments prior to the end of the planned 12 weeks of treatment, you will be asked to have the same measurements when you stop taking the treatments just as would be done at 12 weeks.

ALTERNATIVES TO PARTICIPATION: There are no direct alternatives to your participating in this study. One alternative would be for you to not participate in this research study. If your doctor determines that you testosterone level is below normal, he or she may advise you to be treated with testosterone or possibly an anabolic steroid at doses that should replace levels of missing male hormone.

COSTS TO YOU: There is no cost to you for the study treatment, study-related clinic visits, examinations, or laboratory tests in this study. You will not receive any additional drug once you complete (or discontinue prematurely from) the study. Any medical costs for your treatment outside this study will be charged to you or your health insurance company.

CONFIDENTIALITY: The confidentiality of your medical records for this study will be maintained by the investigators and the Institutional Review Board (IRB). Specific study-related information may be sent to the sponsor who is Unimed Inc. but your name will be deleted. The Food and Drug Administration (FDA) will be allowed access to your medical records. Unless otherwise required by law, the FDA will maintain the confidentiality of your medical records.

RESEARCH-RELATED INJURY: The General Clinical Research Center (GCRC) will provide appropriate medical care for injury resulting from your participation in this study. However, the duration and extent of any medical treatment will be determined by the GCRC Advisory Committee of the General Clinical Research Center. No monetary compensation can be offered.

COMPENSATION: ~~There will be no financial compensation to you for your participation in this study.~~ You will receive $50 after each measurements of body water before the study starts and after you have completed the study. Thus, you will receive $100 for expenses incurred for your having to come to the Medical Center for about 5 hours on each of two occasions.

PROBLEMS OR QUESTIONS: If you ever have questions about this study or in case of research-related injuries, you should contact Fred Sattler at (323) 343-8288, or if you have questions about the rights of a research subject, you should call the Institutional Review Board at (323) 223-2340.

interaction of a number of variables, including genetics, lifestyle factors, chronic disease, hormonal changes, etc. Loss of muscle (sarcopenia) is an important complication of aging. Contributing factor include impaired intake of nutritional energy sources, such as protein, chronic inflammation from underlying medical conditions, and decreased activity due to altered mood, musculoskeletal disorders (e.g., osteoarthritis, osteoporosis), cardiovascular disease (heart failure, stroke), etc.

Defining convenient and effective means to increase muscle mass in the elderly is an important priority in maintaining independence and psychological well being in the elderly. A number of treatment modalities can be considered for therapy of sarcopenia in this population. One attractive therapy involves the potential use of anabolic steroids. The planned study will test the hypothesis that the loss of lean tissue (particularly muscle mass) is the primary mechanism for impaired physical performance (gait, stair climbing, etc.), quality of life, and sense of well-being in frail elderly men and can be corrected during therapy with an oral anabolic steroid.

The specific aims of the study are the following: 1) to determine if there is a dose dependent effect of oxymetholone on lean body mass, muscle mass, physical performance, intra-abdominal fat, tolerability, sexual function, and quality of life in men at risk for sarcopenia and impaired physical performance, 2) to determine the safety of two doses of oxymetholone in elderly men at risk for sarcopenia and frailty.

2. Background: State the background of the study, including a critical evaluation of existing knowledge and the information gaps that this research proposes to fill. Describe previous work that provides a basis for the proposed research and that supports the expectations of obtaining useful information without undue risk to human subjects. Please include relevant citations.

Testosterone and anabolic steroids increase total body lean tissue and fractional synthetic rate of human skeletal muscle protein. At the tissue level, ttestosterone tightly regulates muscle IGF-1 RNA trascription and IGF-1 binding proteins (Urban et al 1995) and may inhibit myostatin (McPherron et al 1997). The positive effects on IGF-1 in muscle are important since up to 80% elderly are prone to deficiency of the growth hormone/IGF-1 axis. In addition, these anabolic derivatives have potent lipolytic properties (Marin et al 1995) and, thus, have the potential to reduce intra-abdominal visceral fat, which also increases in the elderly and is a major risk factor for cardiovascular complications (Matsuzawa et al, 1995; nakamura et al, 1997). Also, anabolic steroids significantly increase bone mineral density (BMD) in persons at risk for osteoporosis or spontaneous fractures (Hassager eet al 1989; Erdtsieck et al 1994). Increasing BMD strengthens the musculoskeletal system and reduces the risk for spontaneous fractures.

Oxymetholone has been selected since it has potent anabolic properties and in studies of wasted patients infected with HIV, treatment with 150mg per day resulted in substantial weight gain [average of 6.1 +/=4.6 to 8.2 +/=6.2 kg] (Hennge et al 1996). In the latter group of patients who are at risk for adverse affects, oxymetholone was well tolerated after more than 6 months of treatment.

We anticipate that the study will demonstrate that significant increases in FFM, muscle area, and functional performance will be achieved during therapy with oxymetholone and that there will be a dose dependent effect. The potential consequences of increases in lean tissue and mobility are substantial. These include improved level of energy, sense of well being, appetite, and sexual function. As a result of increased muscle mass and physical activity, there may be improvements in cardiovascular fitness (ie increased VOZ Max), insulin sensitivity, joint stiffness, etc. As these elderly subjects become less sedentary, the risk of spontaneous fractures from osteoporosis and pulmonary embolism from deep venous thrombosis in the extremities should also diminish. Finally, by improving mobility, this will provide the opportunity for elderly individuals to participate in exercise programs such as walking which have been associated with decreases in serum lipids and risk for coronary events and stroke. These potential benefits should be extremely important for maintaining and restoring health and sense of well being in the elderly. Although documenting many of the benefits enumerated above are beyond the scope of testing for this study, demonstrating that an oral anabolic steroid can augment lean tissue and physical activity will provide the justification to further explore the benefits of this therapy in the elderly.

3. Study Design: Describe the study design (e.g., double blind, crossover, etc.) and sequentially list all procedures, drugs or devices to be used on human subjects. Describe any use of placebos and indicate whether subjects will be randomized in this study. If there are any investigational drugs or biologic agents used in this study, please complete and include Attachment #1 with this application.

This study is a placebo-controlled, double-blind, randomized study, involving frail elderly men. The study will be conducted at LA-USC and Drew University. The study consists of a two week screening period, baseline, and

Research Methods and Procedures

8. Methodology and Data Collection: Describe the research procedures that will be followed. Please indicate those that are experimental and those that may be considered to be standard treatment. Describe all activities involving human subjects and explain the frequency and duration of each activity.

This will be a placebo-controlled, dose-ranging intervention study involving frail elderly men. The study will be conducted at USC and Drew University (Shalender Bhasin, CoPI). The primary endpoint will be an increase in lean tissue (FFM of at least 3.0 kg). Secondary endpoints will measure changes in intra-abdominal fat, increases in strength, and improvements in physical performance associated with study therapy. Tests for safety will be monitored and include serum hemoglobin/hematocrit, liver tests, lipids, and prostatic specific antigen. A treadmill test for aerobic fitness (V02max) at pre-entry will also be monitored for EKG changes which will minimize the risk of cardiovascular complications during strength and power testing (Appendix I).

Measures of body composition will include DEXA scanning for total body and regional lean tissue and fat mass, BIA for body cell mass, and MRI scanning of the abdomen for visceral fat and cross section of the thigh for muscle area. Strength will be measured by the one repetition maximum (1RM) with free weights and leg power will be assessed on the Bassey Leg Extensor Rig. Physical performance will be directly measured using validated tests performed by a certified therapist. Mood and sexual function will be assessed by validated QOL instruments (Appendix IX).

Randomization: Patients will be randomized to one of three regimens for 12 weeks

(1) Placebo (2 tablets per day)
(2) Oxymetholone 50 mg and 1 placebo tablets per day
(3) Oxymetholone 100 mg

To assure comparability of the study groups and that there is not a "center effect", subjects will be assigned by blocked randomization codes at the Drew/King and LA-USC centers. All subjects will be coded with initials and assigned numbers.

Measurements:

Body Composition and fluid status
(a) DEXA for lean body mass, bone mineral density, and fat (total and regional, Appendix VII)
(b) MRI of thigh for muscle cross-sectional area and abdomen for visceral fat (Appendix VII)
(c) Total body water and lean tissue by D20 (heavy water) and extracellular H20 by NaBr (sodium bromide) --Appendix II
(d) Anthropometry (waste/hip ratios)
Strength (Power-Bassey Rig and 1-repetition maximum [1-RM])--Appendix III
Aerobic fitness by V02max testing--Appendix I
Functional Performance--Appendix IV
(a) Up and go test (from standard height with arms folded)--10 meters
(b) Stair climbing time (standard 4 steps to 0.635 meters)
(c) Habitual gait speed over 6.1 meters
(d) Tandem gait speed over 6.1 meters
(e) Weighted (10% body weight) 20 meter walk
(f) Sharpened Romberg test for balance
Quality of life/sense of well being/physical activities/sexual function questionnaires--Appendix IX
Sex hormones (free and total testosterone/DHT/EZ/LH) and myostatin
Safety tests:
(a) Hemoglobin/hematocrit
(b) Fasting lipid panel (total/LDLIHDL cholesterol and triglycerides)
(c) Liver tests (ALT, albumin, alkaline phosphatase, bilirubih)
(d) Prostatic Specific Antigen (PSA) (c) Habitual gait speed over 6.1 meters

9. If your study uses surveys, questionnaires, or psychological tests, please describe the provisions for administering these measures, the mode of administration, the setting and if special training or qualifications are necessary.

ıjects in a private setting in the CRC. They will be given ample time to answer the questions & the research coordinator will be available to answer any questions regarding the questionnaire. The subject will be in the setting by himself.

The Food Diary is simple, and only requires the subject to record his food intake for 3 days on provided forms which include instructions on how to record their intake. The subject will be informed that he may call the research coordinator or the dietician if he has any questions.

10. Please complete the following questions regarding data storage:

a. How will the data be collected and recorded? How will the data be coded to protect personal privacy?	The data will be collected by the research coordinator &/or the principal investigator. The data will then be coded by code numbers. No subject identifiers (e.g., names or hospital numbers) will be on any of the data.
b. How will the data be stored during the study?	The data will stored in locked files with access limited to study personnel. All blood samples will be stored in locked freezers at Charles R. Drew University's laboratory under confidentiality.
c. Who will have access to the data and the data codes? If data with subject identifiers will be released, specify the person(s) and agencies to whom this information will be released	Only the research coordinator and/or the principal investigator will have access to the files. Subject identifiers may be released to the FDA. The files will also be reviewed by the funding agency's (Unimed) monitor(s).
d. What will happen to the data when the study is completed?	According to FDA requirements, the data will be stored in locked cabinets for at least 15 years.

Risk/Benefit Assessment

11. Potential Risks and Discomforts: Describe any potential risks or likely adverse effects of the drugs, biologics, devices or procedures subjects may encounter in the study. State the potential risks – physical, psychological, social, legal or other – connected with the proposed procedures and assess their likelihood and seriousness.

The side effects of oxymetholone include fluid retention, weight gain, hypertension, psychiatric symptoms, nausea, vomiting, diarrhea, lipid abnormalities, hyperglucagonemia, and possibly leukemia, acne, oiliness of skin, breast tenderness and enlargement, and increase in red blood cell count. Liver problems are uncommon at doses being studied. However, there is a possibility of liver problems, such as cholestasis, jaundice, elevated liver function tests, and peliosis hepatis. The long-term effects of oxymetholone on the prostate are not known.

There is minimal risk involved in obtaining a chest x-ray, since the amount of radiation received is far below any clinically significant threshold. The amount of radiation is comparable to less than 0.4 percent of the amount that each radiation worker is allowed to receive from radiation usage each year. This is in the normal range for the amount of radiation exposure from similar diagnostic x-ray procedures.

There is minimal risk involved in obtaining a DEXA scan. The estimated radiation dose from a DEXA scan to the whole body is less than 25 millirads (mrads). A millirad is a unit of measurement for radiation. No amount of radiation is considered completely safe.

There is no known risk from the MRI scan, except in persons with metal fragments or implantable devices such as a pacemaker. However, some people may fee uncomfortable or even claustrophobic (afraid of closed spaces) while lying in the machine. Because MRI scan uses a powerful magnet, individuals with metal fragments or implantable devices, will not undergo this procedure.

The risk of muscle function testing include the possibility of injury and muscle soreness. The risk will be

rocedures.

Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site of venipuncture or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Collecting urine samples at various times during the research study may be inconvenient for some subjects.

There are no known risks associated with drinking D2O or NaBr solutions.

The questions about quality of life may be very personal and some questions some what embarrassing. If subjects feel uncomfortable answering any questions, they may decline to answer those questions.

Other unpredictable side effects besides those listed above may occur. It is important that subjects report any drug side effects to the research study doctor. Long-term (years) side effects are not known at this time.

12. Risk Classification: Please check the level* of risk associated with this study

** According to HHS/FDA regulations minimal risk means, "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." When the risks that are associated with a new procedure or product are unknown, they cannot be classified as minimal.*

☐ minimal ☒ greater than minimal ☐ unknown

13. Safety Precautions for Minimizing Risks: Describe the procedures for minimizing any potential risks. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subject. Where appropriate describe the provisions for monitoring the data collected to ensure the safety of the subjects.

Management of Adverse Events: The following adverse events will be treatment terminating:

(1) New onset heart failure or angina
(2) New hypertension requiring therapy
(3) Increase in Hct to >54%
(4) Sustained increase in PSA to >4 ng/ml on two repeated measures
(5) ALT >5X ULN (upper limits of normal) on repeated measures

Ongoing Safety Monitoring:
Several ongoing safety tests have been included in the study which include the following:

1. Hemoglobin/Hematocrit 2. Fasting Lipid panel 3. Liver panel 4. PSA

14. Benefit Ratio: What is the risk benefit ratio of this research, compared with available alternatives? Describe the potential benefits the subjects may receive as a result of their partipcation in the research and what benefits to society may be expected. *The potential benefits of the research must justify the risks to human subjects. The risk benefit ratio of the research must be at least as favorable for the subjects as that presented by standard treatments for their condition. When comparing the risk/benefit ratio of research with that of available alternatives, the alternative of doing nothing should be included in the analysis.*

There is no guarantee that the patients will benefit from the research study. However, they may benefit from oxymetholone by having increased muscle strength and feeling better. Also, the knowledge gained from the study may help the patients and those who suffer from loss of muscle strength and physical activity.

15. Therapeutic Alternatives: What therapeutic alternative(s) are reasonably available to potential subjects should they choose not to participate in the study? These may be research or non-research-based alternatives.

ct in a language understandable to him. The above representative gives the prospective subject opportunities to ask questions and ample time to discuss participation with family or others before signing the consent. In the informed consent reading and after, recruiters continually emphasize the voluntary nature of the subjects' participation in the study, and that they are free to withdraw from the study at any time with no effect on their medical care.

22. Information Withheld from Subjects: Will any information about the research purpose and design be withheld from subjects? If so, please explain the non-disclosure and describe plans for post-study de-briefing.

N/A

Data Analysis

23. Please delineate the data analysis plans for this study. Include planned statistical analyses and explanation of determination sample size.

Please see the following page.

Charles R. Drew University
Institutional Review Board
Minutes
August 6, 2003

VII OHRP Letter

A. IRB #00-05-030-03 Bhasin "Investigator Initiated Dose Ranging Study of Oxymetholone in Frail Elderly Men"

IRB members were informed by the Director of letter received from Dr.Bhasin in response to allegations non-compliance for this study. A written response is required by Dr. Francis to OHRP by August 22, 2003. The Board discussed the response. Dr. Salehian led the discussion. Dr. Salehian suggested the following questions need to be answered by the investigator.

1. Define hypogonadism in regard to the three terms of 1) sexual and 2nd sexual characteristics; 2) biochemically T and LH levels, and 3) anabolically (muscle and if available bone mass) and answer each question based on this definition. Note: not to mix increased muscle mass as the only measure of androgenic effect.

2. State if it is assumption regarding answer given, specifically the research question of hypogonadism [in terms of sexual function and biochemically T and LH] is not answered, although the anabolic part of hypogonadism was responded to oxymetholone.

3. Question #2 (See page 11 in letter) – you may supplement text be defining in terms of nano gram/dl instead of microgram/dL.

4. Question #2 (See page 12 in letter)-supplement LH data to be presented by each individual as a biochemical androgenic effect of T on gonadotroph cells.

5. Page 9 of Allegation Attachment response, dated July 20, 2003, please answer each allegation 7, 8, 9, 10, 11, 12, 13, and 14 b even if it is necessary to repeat each statement.

A motion made and seconded to accept the report from Dr. Bhasin and to ask for response to the further inquiries as stated.

A quorum of IRB members was present. The motion passed by a vote of 10 in favor, 0 opposed, and 0 abstentions (a total of 10 votes).

APPENDIX D

ORI RESPONSE

In August 2007, a good faith[476] complaint of scientific misconduct was filed under 42 C.F.R. Part 50, Subpart A Responsibility of PHS Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science.[477] The complaint, specifically, is misconduct in the recording and reporting of serum testosterone measurements in the published study, "*Effects of an oral androgen on muscle and metabolism in older, community-dwelling men*."[478] The following document represents the ORI response.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Public Health and Science
Office of Research Integrity
1101 Wootton Parkway, Suite, 750
Rockville MD 20852

Ph. 240-453-8200
FAX 301-594-0043
e-mail: cpascalg@osophs.dhhs.gov
Web: http://ori.dhhs.gov/

CONFIDENTIAL

August 23, 2007

Michael Scally, M.D.
1660 Beaconshire
Houston, Texas 77077-3848

RE: DIO 3765

Dear Dr. Scally:

The Office of Research Integrity (ORI) has received and reviewed the package of letters and other documents that you recently sent by e-mail on August 12, 2007, including two letters to me and one to Dr. Patrick McNeilly of the Office for Human Research Protections (OHRP), also dated August 12.

In your longer (18 page) letter to ORI, you present allegations of scientific misconduct against individuals, not explicitly identified or linked with specific claims of falsification or fabrication, at the Keck School of Medicine, The University of Southern California, and at Charles Drew University School of Medicine in Los Angeles, California. Your concerns date back to at least the 2003 publication by Schroeder *at al.* (*Am. J. Physiol. Endocrinol. Metab.* **284**:E120-E128, 2003) and your complaint to OHRP in 2004.

Your letters indicate that you are deeply concerned about the adverse health consequences associated with cessation of the use of illicit or prescribed anabolic steroids (AAS), particularly the development of hypogonadism. Your original communications with OHRP appeared to focus on the inability or unwillingness of the authors to properly test their patients for testosterone at the end of the 12 week treatment, thereby ensuring that potential hypogonadism would not be detected. Your analyses indicate that the authors should have been aware of the high probability of this outcome after 12 weeks of AAS, and the current literature appears to bear this out. However, it also appears from the OHRP letter to you of November 10, 2004, that this was not a well established outcome of AAS at the time of the original study protocol and publication. In any event, this is a matter for OHRP to review as it deems necessary.

Your 18 page letter attempts to establish that the questioned paper contained data that should have indicated to the authors that the men must have had dramatically lowered testosterone levels

at the end of 12 weeks of treatment even in the absence of direct readings from their sera. However, even if this were the case, and by no means do I believe you have established it, this would not represent the intentional reporting of falsified data, or constitute an allegation of scientific misconduct.

Your letter also discusses 12 week testosterone levels from four (or in one report three) subjects as being inconsistent with baseline levels of a larger group of nine individuals. You develop a substantial statistical argument to show the extremely low probability that testosterone values from the four, or three, subjects could have been obtained from the same population of subject used to obtain a quite different mean testosterone level at baseline. I would agree with you, but also could find no language that actually linked the four (or three) subjects used to measure testosterone at baseline, six, and twelve weeks with the cohort in the Schroeder *at al.* paper. In FOIA D #027, it was stated that "the investigators in the above referenced study did measure serum testosterone levels in four men treated with oxymetholone at baseline and after 6 and 12 weeks of treatment. In these subjects, serum testosterone levels did not show a significant change from baseline." Since the Schroeder *at al.* paper states that 12 week testosterone levels were not obtained in that study, it must be assumed that the two sets of numbers were obtained from different groups of subjects.

For these reasons, your concerns do not rise to the level of an allegation of research (or scientific) misconduct at the PHS level. This is not to say that your concerns about the adverse consequences of discontinuing AAS are without merit; they clearly warrant attention by the medical community. I suggest that you focus your undoubted expertise and knowledge on a more positive approach to informing the public and medical community of these important issues.

Sincerely,

Chris B.Pascal, J.D.
Director
Office of Research Integrity

cc. Patrick McNeilly
Compliance Oversight Coordinator
OHRP

Kristina
Borror
Division Director
OHRP

APPENDIX E

OHRP RESPONSE

In August 2007, resubmission of alleged violations of 45 C.F.R. § 46, Subpart A, Protection of Human Subjects based on additional information obtained through the FOIA was filed for the published study, "*Effects of an oral androgen on muscle and metabolism in older, community-dwelling men*."[479] The new allegations include the failure to conduct research consistent with 45 C.F.R. § 46.111.[480] The informed consent process for the research failed to include the elements required by DHHS regulations at 45 C.F.R. § 46.116.[481] The following document represents the OHRP response.

The allegations include the failure to use a sound research design, failure to use sound research methodology, and not providing a fully informed consent. The research design did not take into consideration that the use of oxymetholone causes a disruption of the hypothalamic-pituitary-testicular axis (HPTA), resulting in a state of hypogonadism. The research methodology did not make provisions for data monitoring of concern to the safety of the patients, specifically for testosterone levels during oxymetholone administration and at the end of the 12-week treatment period, thus failing to monitor for a possible hypogonadal state in the subjects. Without consideration in the research design, research methodology, and data monitoring for hypogonadism during and after AAS administration, it is not possible to give a fully informed consent upon which one can make a decision to participate in the clinical trial.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

SEP 25 2007

Michael Scally, M.D.
1660 Beaconshire
Houston, Texas 77077-3848

Dear Dr. Scally:

Thank you for your letters to Secretary Michael Leavitt, former Assistant Secretary for Health, Dr. John Agwunobi, and staff of the Office for Human Research Protections (OHRP) regarding research at various institutions involving the therapeutic use of anabolic steroids (AAS). I have been asked to respond directly to you.

In your letters you present allegations against several clinical investigators and institutions of scientific misconduct and violations of the HHS protection of human subjects regulations; specifically, you allege violations of the regulatory provisions at 45 CFR 46.111 and 45 CFR 46.116, which require that risks to subjects are minimized and that subjects are informed of foreseeable risks of the research. The current allegations are similar to the allegations that originally were reviewed by OHRP in an investigation of the University of Southern California (USC) and Charles R. Drew University School of Medicine and Science (CDU). The investigation of USC/CDU was closed on November 5, 2004, as the allegations could not be substantiated.

Your letters indicate that you are deeply concerned about the adverse health consequences associated with the cessation of the use of prescribed AAS and particularly with the development of hypogonadism. You assert that these investigators and institutions did not warn or protect research subjects from the risk of hypogonadism associated with the cessation of therapeutic doses of AAS.

The HHS protection of human subjects regulations are designed, in part, to protect research subjects from and inform them about known risks that they may incur while participating in a research study. From OHRP's examination of this issue, we have found that the mainstream medical community currently does not recognize that hypogonadism results from the cessation of FDA approved doses of therapeutic AAS. Therefore, it would be reasonable for an institutional review board (IRB) not to attempt to minimize the risk of developing hypogonadism after ceasing the use of therapeutic AAS, and to approve an informed consent process that does not address the development of hypogonadism as a risk of the research, because this risk is not recognized by the mainstream medical community.

Because the allegations you raise do not appear to involve violations of the HHS protection of human subjects regulations, OHRP anticipates no further involvement in this matter.

OHRP appreciates your concern about the protection of human research subjects. Please do not hesitate to contact me at (240) 453-8218 or paul.andreason@hhs.gov should you have any questions.

Sincerely,

Paul J. Andreason, M.D.
CAPT, USPHS
Compliance Oversight Coordinator
Division of Compliance Oversight
Office for Human Research Protections

APPENDIX F

REFERENCE INTERVAL TABLES

Test	Reference Range
Alanine aminotransferase (ALT, SGPT) Levels are extremely increased in cases of liver cell necrosis of any cause, right heart failure, acute anoxia, extensive trauma, or left heart failure. A slightly high level may indicate cirrhosis, obstructive jaundice, liver tumors, extensive myocardial infarction, myositis, muscular dystrophy, fatty liver, chronic alcohol abuse, or severe pancreatitis. Levels will by low in cases of pyridoxal phosphate deficiency	
Female	7-30 U/liter
Male	10-55 U/liter
Albumin There is no naturally occurring hyperalbuminemia. Any condition that results in the decrease of plasma water will increase the concentration of all plasma proteins, including albumin. Low concentrations of blood albumin may be due to acute and chronic inflammation, decreased synthesis by the liver, increased loss via body surfaces, increased catabolism, or increased blood volume. *albumin is the principal oncotically active component of plasma. As the major plasma protein, albumin acts as a nitrogen pool. Its role in transporting bilirubin, bile acids, metal ions, and drugs will be markedly affected by variations in concentrations.	3.1-4.3 g/dl
Alkaline phosphatase (adult) Origins of the major phosphatases are liver, bone, intestine, endometrium, and lung. Ingestion of a meal increases the intestinal isoenzyme of alp in serum, especially in individuals who are blood type o or b and who are Lewis-positive secretors. Increased levels of alp may indicate increased bone metabolism (during healing of fracture, primary and secondary hyperparathyroidism, osteomalacia, or juvenile rickets). May also indicate bone disease, renal disease, or liver disease. Low levels may indicate hypothyroidism, scurvy, gross anemia, vitamin b12 deficiency or nutritional deficiency of zinc or magnesium.	
Female	30-100 U/liter
Male	45-115 U/liter
Androstenedione (adult) Androstenedione is a major precursor in the biosynthesis of androgens and estrogens. It is produced in adrenals and gonads and serves as prohormone for testosterone and estrone. The test is useful in conjunction with other tests in the evaluation and management of androgen disorders	50-250 ng/dl
Aspartate aminotransferase (AST, SGOT) Increased levels may indicate liver cell necrosis or injury of any cause, including cholestatic and obstructive jaundice, chronic hepatitis, or drug-induced injury to liver. May also be associated with hepatic metastases and hepatoma, necrosis or trauma to	

heart or skeletal muscle, inflammatory disease of heart or skeletal muscle, heart failure, Forbes's disease, heat stroke, hypothyroidism, intestinal obstruction, lactate acidosis, or toxic shock syndrome. Also distinguishes neonatal hepatitis from biliary atresia.	
Female	9-25 U/liter
Male	10-40 U/liter
Bilirubin, direct High serum blood levels are associated with intrahepatic and extrahepatic biliary tree obstruction, hepatocellular damage, cholestasis, Dubin-Johnson syndrome, or rotor's syndrome.	0.0-0.4 mg/dl
Bilirubin, total High serum levels may indicate hepatocellular damage (inflammatory, toxic, neoplastic), intrahepatic and extrahepatic biliary tree obstruction, hemolytic diseases, fructose intolerance, hypothyroidism or neonatal physiological jaundice	0.0-1.0 mg/dl
Calcium High blood calcium levels may indicate primary and tertiary hyperparathyroidism, malignant disease with bone involvement (in particular metastatic carcinoma of the breast, lung, kidney, multiple myeloma, lymphomas, and leukemia), vitamin d intoxication, milk-alkali syndrome, Paget's disease with immobilization, thyrotoxicosis, acromegaly, diuretic phase of acute tubular necrosis or dehydration. Low levels of calcium may indicate hypoparathyroidism; vitamin d deficiency, chronic renal failure, magnesium deficiency, prolonged anticonvulsant therapy, acute pancreatitis, anterior pituitary hypofunction, hypoalbuminemia, or inadequate nutrition.	8.5-10.5 mg/dl
Carbon dioxide content, total High levels may indicate respiratory acidosis caused by poor gas exchange or depression of respiratory center; generalized respiratory disease; metabolic acidosis (after severe vomiting in pyloric stenosis, hypokalemic states, or excessive alkali intake). Low levels may indicate compensated respiratory alkalosis, metabolic acidosis in diabetes mellitus, renal glomerular or tubular failure, renal tubular acidosis and intestinal loss of alkali with coexisting increase in c1 and normal anion gap	24-30 mmol/liter
Chloride High chloride levels may be attributed to dehydration, renal tubular acidosis, acute renal failure, diabetes insipidus, metabolic acidosis associated with prolonged diarrhea with loss of nahco3, respiratory alkalosis, and some cases of primary hyperparathyroidism. Low serum chloride levels may be due to excessive sweating, prolonged vomiting from any cause or gastric suction, persistent gastric secretion, salt-losing nephritis, aldosteronism, potassium depletion associated with alkalosis, respiratory acidosis	100-108 mmol/liter
Cholesterol High total cholesterol levels may indicate familial or polygenic hyperlipoproteinemia types IIa and IIb, hyperlipidemia, hyperlipoproteinemias secondary to hepatocellular disease, intra- and extrahepatic cholestasis, chronic renal failure, malignant neoplasms of pancreas and prostate, hypothyroidism, gout, ischemic heart disease, pregnancy, diabetes, alcoholism, analbuminemia, dysglobulinemia, anorexia nervosa, idiopathic hypercalcemia, acute intermittent porphyria, or isolated hgh deficiency. Low levels may be associated with lipoprotein deficiency, hepatocellular necrosis, malignant neoplasm of liver, hyperthyroidism, malabsorption, malnutrition, megaloblastic	

anemias, chronic obstructive lung disease, mental retardation, rheumatoid arthritis, or intestinal lymphangiectasia. *secondary disorders that elevate cholesterol levels should be ruled out prior to initiating therapy with cholesterol-lowering drugs. *factors that have variable effects on cholesterol levels in different people include posture before and at time of blood sampling, a recent meal, emotional stress, and menstrual cycle.	
Desirable	<200 mg/dl
Borderline high	200-239 mg/dl
High	>239 mg/dl
Creatinine High serum or plasma levels may indicate renal function impairment, both acute and chronic; active acromegaly and gigantism, hyperthyroidism, and meat meals	0.6-1.5 mg/dl
Dehydroepiandrosterone (DHEA) sulfate (adult) Decreased levels may be associated with increased age in men & women, hyperlipidemia, psychosis, or psoriasis. Weakly androgenic	
Male	10-619 µg/dl
Female	
Premenopausal	12-535 µg/dl
Postmenopausal	30-260 µg/dl
Estradiol Estradiol is the most active of endogenous estrogens. The test is of value, together with gonadotropins, in evaluating menstrual and fertility problems in adult females. Measurement is also useful in the evaluation of gynecomastia or feminization states due to estrogen &/or producing tumors.	
Female	
Menstruating	
Follicular phase	50-145 pg/ml
Midcycle peak	112-443 pg/ml
Luteal phase	50-241 pg/ml
Postmenopausal	<59 pg/ml
Male	<50 pg/ml
Follicle-stimulating hormone (FSH) In hypogonadism, FSH and LH levels lower than normal for the patient's age indicate hypothalamic or pituitary problems; higher levels indicate a primary gonadal defect	
Female	
Menstruating	
Follicular phase	3.0-20.0 U/liter
Ovulatory phase	9.0-26.0 U/liter
Luteal phase	1.0-12.0 U/liter
Postmenopausal	18.0-153.0 U/liter
Male	1.0-12.0 U/liter
Globulin High levels may be associated with chronic hepatitis, plasma cell dyscrasias/	2.6-4.1 g/dl

lymphoproliferative disorders, cirrhosis, chronic liver diseases, chronic infections or certain autoimmune disorders. Low levels may indicate immune deficiency or suppression or lymphoproliferative disorder. Decreases in all fractions may be seen in bulk loss of proteins into the gut.	
Glucose, fasting Serum glucose levels may be high due to diabetes mellitus, strenuous exercise, increased epinephrine, pancreatic disease or an endocrine disorder. A high serum level may also be related to acute myocardial infarction or severe angina, chronic liver disease, or chronic renal disease.	70-110 mg/dl
(gamma)-Glutamyltransferase (GGT) Very high levels can be associated with obstructive liver disease and posthepatic obstruction. Moderately high levels may indicate liver disease (inflammation, cirrhosis, space-occupying lesions), infectious mononucleosis, renal transplant, hyperthyroidism, myotonic dystrophy, diabetes mellitus, pancreatitis, or alcohol-induced liver disease. Low GGT levels will indicate hypothyroidism. *useful marker for pancreatic cancer, prostatic cancer, and hepatoma because levels reflect remission and recurrence.	
Male	1-94 U/liter
Female	1-70 U/liter
Growth hormone (resting) Secretion of GH is episodic and pulsatile; highest values occur during periods of deepest sleep. Ability to secrete GH in response to a conventional challenge declines with age. Random levels of GH provide little diagnostic information; GH secretion is best assessed during tests that stimulate or suppress release. Patients with GH-producing pituitary disorders often release GH in response to TRH or GnRH; and patients with suspected GH deficiencies have subnormal responses to stimulation tests (i.e. GH stimulation test after arginine, insulin, l-dopa, glucagon, propanolol and insulin tolerance test.)	2-5 ng/ml
Hemoglobin A_{1C} Glycated hemoglobin concentration appears to reflect the mean blood glucose concentration over the previous 4-8 wks. This test, while not useful for the diagnosis of diabetes mellitus, has been shown to be useful in monitoring its long-term control. Glycated hemoglobins are increased as a reflection of hyperglycemia during the lifespan of erythrocytes	3.8-6.4%
High-density lipoprotein cholesterol, as major risk factor Epidemiological studies demonstrate the inverse association between HDL-c levels and the incidence and prevalence of coronary heart disease (CHD). It is suggested that for every 5 mg/dl decrease in HDL-c below the mean, the risk of CHD increases 25%. Another approach in assessing CHD risk is to calculate the ratio of HDL-c to either LDL-c or total cholesterol. The following primary disease states can lead to secondary decrease in HDL-c: uncontrolled diabetes, premature coronary heart disease, hepatocellular disorders, cholestasis, nephrotic syndrome, and chronic renal failure.	<35 mg/dl
Insulin Decreased serum levels indicate inadequately treated type I diabetes mellitus. High serum levels may indicate insulin overdose, insulin resistance syndromes, or endogenous hyperinsulinemia	2-20 U/ml

Lactate dehydrogenase (LDH) Extremely high levels may indicate megaloblastic and pernicious anemia, extensive carcinomatosis, viral hepatitis, shock, hypoxia or extreme hyperthermia. Very high levels are associated with cirrhosis, obstructive jaundice, renal diseases, neoplastic diseases, skeletomuscular diseases, or congestive heart failure. Mildly high levels are associated with any cellular injury that results in loss of cytoplasm, myocardial or pulmonary infarction, leukemias, hemolytic anemias, hepatitis (nonviral), sickle cell disease, lymphoma, renal infarction, or acute pancreatitis.	110-210 U/liter
Lipoprotein(a)	0-30 mg/dl
Low-density lipoprotein cholesterol LDL encompasses all of the lipoproteins with density greater than 1.006 kg/l and less than or equal to 1.063 kg/l. High levels may indicate primary hyperlipoproteinemia types IIa and IIb; tendon and tuberous xanthomas, corneal arcus, and premature coronary heart disease. The following diseases can lead to secondary elevation of LDL-c: hyperlipoproteinemia secondary to hypothyroidism, nephrotic syndrome, hepatic obstruction, hepatic disease, pregnancy, anorexia nervosa, diabetes, chronic renal failure, and Cushing's syndrome.	
Desirable	<130 mg/dl
Borderline high risk	130-159 mg/dl
High risk	greater than or equal to 160 mg/dl
Iron High serum levels may indicate pernicious, aplastic, and hemolytic anemias; hemochromatosis, acute leukemia, lead poisoning, acute hepatitis, vitamin b6 deficiency, excessive iron supplementation/therapy, repeated transfusions, or nephritis. Low serum iron levels may indicate iron-deficiency anemia, remission of pa, acute and chronic infection, carcinoma, nephrosis, hypothyroidism, or postoperative state. *symptoms of iron poisoning include abdominal pain, vomiting, bloody diarrhea, cyanosis, lethargy, and convulsions. Levels may vary widely for an individual within the same day or from day to day.	45-180 ug/dL (MALES & FEMALES).
Luteinizing hormone (LH) Test used to determine the preovulatory LH surge; also provides an integrated picture of LH secretion throughout the day. Shows pituitary or hypothalamic impairment or overproduction	
Female	
Menstruating	
Follicular phase	2.0-15.0
Ovulatory phase	22-105
Luteal phase	0.6-19
Postmenopausal	16-64
Male	2.0-12.0
Magnesium Mg plays a vital role in glucose metabolism by facilitating the formation of muscle and liver glycogen from blood-borne glucose. Also participates as a cofactor in the breakdown of glucose, fatty acids, and amino acids during energy metabolism. High	1.4-2.0 meq/liter

serum levels may indicate dehydration, renal insufficiency, uncontrolled diabetes mellitus, adrenocortical insufficiency, Addison's disease, hypothyroidism or lupus erythematosus. Phytate, fatty acids, and an excess of phosphate impair mg absorption. Symptoms of deficiency usually do not occur until serum levels are <1.0 meq/l. Symptoms of severe depletion are weakness, irritability, tetany, EKG changes, delirium, and convulsions.	
Phosphorus, inorganic (adult) Serum phosphorus concentrations have a circadian rhythm (highest level in late morning, lowest in evening) and are subject to rapid change secondary to environmental factors such as diet (carbohydrate), phosphate-binding antacids, and fluctuations in growth hormone, insulin, and renal function. High levels may indicate osteolytic metastatic bone tumors, myelogenous leukemia, milk-alkali syndrome, vitamin d intoxication, healing fractures, renal failure, hypoparathyroidism, pseudohypoparathyroidism, diabetes mellitus with ketosis, acromegaly, portal cirrhosis, pulmonary embolism, lactic acidosis or respiratory acidosis.	2.6-4.5 mg/dl
Potassium High potassium levels are associated with reduced renal excretion of potassium or redistribution of potassium in the body (i.e. Massive hemolysis, severe tissue damage, severe acute starvation-anorexia nervosa, hyperkinetic activity, malignant hyperpyrexia following anesthesia, hyperkalemic periodic paralysis, and dehydration).	3.4-4.8 mmol/liter
Progesterone The diagnostic value of this test lies in its detection of ovulation and in the evaluation of the function of the corpus luteum. Serial sampling during the menstrual cycle is required. During menopause, levels drop to 0	
Female	
Follicular phase	<1.0 ng/ml
Midluteal phase	3-20 ng/ml
Male	<1.0 ng/ml
Prolactin May help assess Prolactin reserve and abnormal Prolactin secretion by the pituitary. May indicate pituitary tumors.	
Female	
Premenopausal	0-20 ng/ml
Postmenopausal	0-15 ng/ml
Male	0-15 ng/ml
Prostate-specific antigen (PSA) PSA is prostate-tissue specific, not prostate-cancer specific. Used for early detection of the recurrence of prostatic cancer. The test is of great value as a marker in the follow-up of patients at high risk for disease progression. PSA values increase with age.	
Female	<0.5 ng/ml
Male	
<40 yr old	0.0-2.0 ng/ml
greater than or equal to 40 yr old	0.0-4.0 ng/ml
Prostate-specific antigen (PSA), free, in males 45-75 yr old, with PSA values between	>25% associated with

4 and 20 ng/ml	benign prostatic hyperplasia
Protein, total High blood levels may be associated with anabolic steroid use, androgens, corticosteroids, coritcotropin, epinephrine, insulin, progesterone, or thyroid preparations. Severe protein deficiency, chronic liver disease, malabsorption syndrome, and malnutrition may also lead to abnormal levels. Serum total protein decreases in the third trimester of pregnancy.	6.0-8.0 g/dl
Sodium High serum levels are associated with water loss in excess of salt through skin, lungs, GI tract, and kidneys. Also may indicate increased renal sodium conservation in hyperaldosteronism, Cushing's syndrome or disease, inadequate water intake because of inadequate thirst mechanism, dehydration, or excessive saline therapy. Low sodium levels may indicate low sodium intake, sodium losses due to vomiting, diarrhea, excessive sweating with adequate water intake and inadequate salt replacement, diuretics abuse, or salt-losing nephropathy	135-145 mmol/liter
Somatomedin C (Insulin-like growth factor I) Blood concentrations of IGF-1 are constant during the day and after eating. In acromegaly, the test may serve as an indicator of the severity of the disease; serial determinations may be used to monitor efficacy of treatment. In dwarfism IGF-1 may be used to determine the response to GH therapy. Concentrations of IGF-1 rise during the first year of life, reaching the highest values in preadolescent or early adolescent years. Normal values tend to decline progressively until age 50	
16-24 yr	182-780 ng/ml
25-39 yr	114-492 ng/ml
40-54 yr	90-360 ng/ml
>54 yr	71-290 ng/ml
Testosterone, total (morning sample) This test is a measure of total circulating testosterone, both protein bound and free. In adult men, serum levels peak in the early morning, decreasing 25% to the evening minimum. Levels increase after exercise and decrease after immobilization and after glucose load. Progressive decreases begin after age 50	
Female	6-86 ng/dl
Male	270-1070 ng/dl
Testosterone, unbound (morning sample) Free (nonprotein-bound) testosterone is independent of changes in concentrations of the principal testosterone transport protein, sex hormone-binding globulin.	
Female	
20-40 yr	0.6-3.1 pg/ml
41-60 yr	0.4-2.5 pg/ml
61-80 yr	0.2-2.0 pg/ml
Male	
20-40 yr	15.0-40.0 pg/ml
41-60 yr	13.0-35.0 pg/ml

61-80 yr	12.0-28.0 pg/ml
Thyroid-stimulating hormone (TSH) First-line test for hyper- and hypothyroidism. Test is considered by some to be the preferred screening test for evaluation of thyrometabolic states. Moderately high TSH is often found in euthyroid patients during treatment of hyperthyroidism.	0.5-5.0 U/ml
Thyroxine, total (T_4) Used in conjunction with other tests to measure thryoid function. T_4 testing is frequently used when TSH levels are abnormally high or low. In hypothyroidism, total serum t_4 falls before t_3. High serum levels may represent hyperthyroidism.	4.5-10.9 g/dl
Transferrin Transferrin is the major plasma transport protein for iron. High serum levels may indicate iron deficiency (high levels often precede the appearance of anemia by days to months). Serum ferritin levels fall with iron deficiency and with generalized malnutrition but remain normal in the presence of inflammation and iron deficiency	191-365 mg/dl
Triglycerides (fasting) Increased triglyceride levels indicate hyperlipoproteinemia types I, IIb, III, IV, and V due to familial or sporadic endogenous hypertriglyceridemia. The following primary disease states or conditions can lead to secondary elevation of triglycerides: obesity, impaired glucose tolerance, viral hepatitis, alcoholism, alcoholic cirrhosis, biliary cirrhosis, acute and chronic pancreatitis, extrahepatic biliary obstruction, nephrotic syndrome, chronic renal failure, essential hypertension, acute myocardial infarction, chronic ischemic heart disease, cerebral thrombosis, hypothyroidism, diabetes mellitus, gout, pregnancy, glycogen storage diseases types I, II, III, and IV, down syndrome, respiratory distress syndrome, Werner's syndrome, anorexia nervosa, or idiopathic hypercalcemia. Low levels of triglycerides may indicate chronic obstructive lung disease, brain infarction, hyperthyroidism, hyperparathyroidism, lactosuria, malnutrition, malabsorption syndrome, intestinal lymphangiectasia or end-stage parenchymal liver disease.	40-150 mg/dl
Triiodothyronine, total (T_3) Used in conjunction with other tests to measure thyroid function. High serum levels may indicate hyperthyroidism while low levels may indicate hypothyroidism. At least 80% of circulating T_3 is derived from monodeiodination of T_4 in peripheral tissues. T_3 is 4 to 5 times more potent in biological systems than T_4	60-181 ng/dl
Urea nitrogen (BUN) (adult) High serum blood levels may indicate impaired kidney function associated with an increase with age or protein content of diet.	8-25 mg/dl
Uric acid High serum levels may indicate gout, renal failure, leukemia, lymphoma, psoriasis, polycythemia, multiple myeloma, kidney disease, and or chronic lead nephropathy. Associated with hyperlipidemia, obesity, hypertension, arteriosclerosis, diabetes mellitus, hypoparathyroidism, acromegaly, and liver disease.	
Male	3.6-8.5 mg/dl
Female	2.3-6.6 mg/dl

Differential blood count	Reference Range
Neutrophils	45-75%
Bands	0-5%
Lymphocytes	16-46%
Monocytes	4-11%
Eosinophils	0-8%
Basophils	0-3%
Erythrocyte count Red Blood Cell count; filled with hemoglobin and specialized for carrying O_2 and CO_2 (adult)	
Male	4.50-5.30 X $10^6/mm^3$
Female	4.10-5.10 X $10^6/mm^3$
Ferritin Surplus iron is stored as Ferritin, primarily in the liver	
Male	30-300 ng/ml
Female	10-200 ng/ml
Folate (folic acid) Water soluble vitamin involved with amino acid metabolism & transfer of single-carbon units in nucleic acid	
Normal	3.1-17.5 ng/ml
Borderline deficient	2.2-3.0 ng/ml
Deficient	<2.2 ng/ml
Excessive	>17.5 ng/ml
Hematocrit (adult) % of Red Blood Cells present in total blood	
Male	37.0-49.0
Female	36.0-46.0
Hemoglobin (adult) Oxygen-carrying compound of blood. Numerical value of hemoglobin present in Red Blood Cells	
Male	13.0-18.0 g/dl
Female	12.0-16.0 g/dl
Iron Constituent of hemoglobin (transport of oxygen in blood) and enzymes involved in energy metabolism	30-160 g/dl
Leukocyte count (WBC) White Blood Cell (WBC); Central to the immune system that defends against infection	4.5-11.0X$10^3/mm^3$
Mean corpuscular hemoglobin (MCH)	25.0-35.0 pg/cell

Value is calculated from hemoglobin and erythrocyte count. MCH= Erc÷Hb	
Mean corpuscular hemoglobin concentration (MCHC) Mean cell hemoglobin concentration is calculated from Hb and hematocrit (Hct) MCHC= Hct÷Hb	31.0-37.0 g/dl
Mean corpuscular volume (MCV) (adult) Mean cell volume may not be reliable when a large number of abnormal erythroctes or a dimorphic population of erythrocytes is present. It may also be calculated from the hematocrit and erythrocyte count MCV= Erc÷Hct	
Male	78-100 m^3
Female	78-102 m^3
Platelet count Helps mediate the blood clotting that prevents loss of blood after injury	150-350X10^3/mm^3
Platelet, mean volume	6.4-11.0 m^3

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manufacturers of oxymetholone. Additional support was provided by National Institutes of Health Grants 1RO1 AG-14369-01, 1RO1 DK-59627-01, 2RO1 DK-49296-02A, and 1RO1 DK-49308-04, the Clinical Trials Unit Grant U01-DK-54047, RCMI Clinical Research Infrastructure Initiative (P20 RR-11145), and Research Center for Minority Institutions Grants G12 RR-03026 and U54 RR-14616.

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350 The exact quote is the following: That more than 90% of the gains in muscle mass and strength were achieved in just 6 weeks could be beneficial to individuals with physical limitations, frailty, or catabolic illness and associated muscle wasting because the long-term safety of androgen supplementation for cardiovascular and prostatic health is unknown. In addition, short-term treatment with potent anabolic androgens may "jumpstart" the anabolic process for improving muscle mass and skeletal muscle strength until these individuals are capable of engaging in resistance exercises, a potent stimulus for myofibrillar muscle protein synthesis and proven means to significantly increase muscle quality and physical function even in nonagenarians. Also, the authors state, "We speculated that if short-term benefits could be achieved, other potentially safer treatments such as resistance exercise could then be implemented to sustain or even augment the early changes achieved with androgen treatment."

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Supported primarily by funding from: National Center for Research Resources General Clinical Research Center (MOI RR-430), National Institutes of Health Grants: 1 RO1 AG-14369-01, 1 RO1 DK-59627-01, 2RO1 DK-49296-02A, 1801 DK-49308-04, Clinical Trials Unit Grant U01-DK-54047, RCMI Clinical Research Infrastructure Initiative (P20 RR-11145), and Research Center for Minority Institutions Grants G12 RR-03026 and U54 RR-14616.

Researchers named from the University of Southern California: E. Todd Schroeder, Carmen Martinez, S. Victoria Jaque, Michael Terk, Fred R. Sattler, and Colleen Azen; Charles Drew University School of Medicine: Atam Singh, Shalender Bhasin, Thomas W. Storer, Tina Davidson, and Indrani Singa-Hikim.

361 45 C.F.R. § 46.111(a)(6) Criteria for IRB approval of research. (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

362 Office for Human Research Protections, 11/05/2004 University of Southern California - Health Science/Charles R. Drew University, Available at: http://www.hhs.gov/ohrp/detrm_letrs/YR04/nov04c.pdf. The determination letter was for Human Research Subject Protections Under Federalwide Assurance (FWA) 5906 and FWA 2736. Recipients of the letter were Cornelius W. Sullivan, Ph.D., Vice Provost for Research, University of Southern California - Health Science, 300 Bovard - University Park Campus, Los Angeles, CA, and Harry E. Douglas, III, D.P.A., Interim President, Charles R. Drew University, School of Medicine and Science, 1731 East 120th Street, Los Angeles, CA.

363 OHRP, Available at: http://ohrp.osophs.dhhs.gov/detrm_letrs/lindex.htm.

364 See Appendix FOIA Documents, FOIA#025.

365 See Appendix FOIA Documents, FOIA#019.

366 See Appendix FOIA Documents, FOIA#026.

367 See Appendix FOIA Documents, FOIA#029.

368 56 Fed Reg 28012 (1991) (codified at 45 C.F.R. §§ 46.101-46.115), 56 Fed Reg 28012 (1991) (codified at 45 C.F.R. §§ 46.116-46.409).

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377 45 C.F.R. § 46.111(a)(1)(i) Criteria for IRB approval of research. (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

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381 See Appendix FOIA Documents, FOIA#026.

382 See Appendix FOIA Documents, FOIA#031-#032.

383 See Appendix FOIA Documents, FOIA#026.

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393 45 C.F.R. § 46.111(a)(2) Criteria for IRB approval of research. (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

394 See Appendix FOIA Documents, FOIA#028.

395 See Appendix FOIA Documents, FOIA#028.

396 See Appendix FOIA Documents, FOIA#027.

397 See Appendix FOIA Documents, FOIA#027, Footnote 1. None of the previous studies involving androgen administration in older men (Snyder et al, 1999; Tenover 2000; Tenover 1992; Morley et al, 1993; Sih et al, 1997; Kenny et al, 2001; Marin et al, 1992; Maria et al, 1995) or men with chronic illness (Grinspoon et al, 1998; Hengge et al, 2003; Strawford et al, 1999; Schols et al, 1995; Hurtado et al, 1993), or funded by NIH or pharmaceutical companies, have followed subjects after treatment discontinuation.

398 See Appendix FOIA Documents, FOIA#027.

399 See Appendix FOIA Documents, FOIA#027.

400 See Appendix FOIA Documents, FOIA#027, Footnote 1.

401 Sheffield-Moore M, Urban RJ, Wolf SE, et al. Short-term oxandrolone administration stimulates net muscle protein synthesis in young men. J Clin Endocrinol Metab 1999;84:2705-11.

402 See Appendix FOIA Documents, FOIA#031-#032.

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406 See Appendix FOIA Documents, FOIA#028.

407 See Appendix FOIA Documents, FOIA#027.

408 45 C.F.R. § 46.111(a)(3) Criteria for IRB approval of research. (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.

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427 42 C.F.R. § 93.210 Good faith as applied to a complainant or witness, means having a belief in the truth of one's allegation or testimony that a reasonable person in the complainant's or witness's position could have based on the information known to the complainant or witness at the time. An allegation or cooperation with a research misconduct proceeding is not in good faith if made with knowing or reckless disregard for information that would negate the allegation or testimony.

428 42 CFR part 50, subpart A, ''Responsibilities of Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science,'' has been replaced by 42 CFR part 93, ''Public Health Service Policies on Research Misconduct.''

429 See Appendix M ORI Response.

430 (3*457 + 6X)/9 = 360; 1371 + 6X = 3240; 6X = 1869; X = 312, checking the math: (1371 + 1872)/9 = 360.

431 (4*457 + 5X)/9 = 360; 1828 + 5X = 3240; 5X = 1412; X = 282, checking the math: (1828 + 1410)/9 = 360.

432 45 C.F.R. 46.102(i). The concept of minimal risk and the principle of informed consent are the key means by which US federal regulations seek to protect the rights and welfare of the individual in the research setting. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

433 See Appendix FOIA Documents, FOIA#029.

434 See Appendix FOIA Documents, FOIA#029.

435 See Appendix FOIA Documents, FOIA#034.

436 See Appendix FOIA Documents, FOIA#005.

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466 The Endocrine Society is the world's largest and most active professional organization of endocrinologists in the world. Founded in 1916, the Society is internationally known as the leading source of state-of-the-art research and clinical advancements in endocrinology and metabolism. The Endocrine Society is an international body with 13,000 members from over 85 countries. The Society publishes four major peer-reviewed journals about endocrinology and metabolism - The Journal of Clinical Endocrinology and Metabolism, Endocrinology, Molecular Endocrinology, and Endocrine Reviews. Dr. Scally is a full member of The Endocrine Society.

467 The American Association of Clinical Endocrinologists (AACE) was founded in 1991. Members of AACE are physicians with special education, training and interest in the practice of clinical endocrinology. All members of AACE are physicians (MD or DO). Members of AACE are recognized clinicians, educators and scientists, many of whom are affiliated with medical schools and universities that contribute on a regular and continuing basis to the scientific literature on endocrine diseases.

468 The American College of Sports Medicine (ACSM) was founded in 1954. As the largest sports medicine and exercise science organization in the world, ACSM has more than 20,000 International, National, and Regional Chapter members. The American College of Sports Medicine promotes and integrates scientific research, education, and practical applications of sports medicine and exercise science to maintain and enhance physical performance, fitness, health, and quality of life.

469 The 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV is published in Antiviral Therapy. Antiviral Therapy is the first international journal solely devoted to the clinical development and use of antiviral agents. Antiviral Therapy is an official publication of the International Society for Antiviral Research. The International Society for Antiviral Research (ISAR) was formally established on May 14, 1987. ISAR has become internationally recognized as an organization for scientist in the field and as offering the premiere scientific meeting on antiviral research.

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Supported primarily by funding from: National Center for Research Resources General Clinical Research Center (MOI RR-430), National Institutes of Health Grants: 1 RO1 AG-14369-01, 1 RO1 DK-59627-01, 2RO1 DK-49296-02A, 1801 DK-49308-04, Clinical Trials Unit Grant U01-DK-54047, RCMI Clinical Research Infrastructure Initiative (P20 RR-11145), and Research Center for Minority Institutions Grants G12 RR-03026 and U54 RR-14616.

Researchers named from the University of Southern California: E. Todd Schroeder, Carmen Martinez, S. Victoria Jaque, Michael Terk, Fred R. Sattler, and Colleen Azen; Charles Drew University School of Medicine: Atam Singh, Shalender Bhasin, Thomas W. Storer, Tina Davidson, and Indrani Singa-Hikim.

474 Office for Human Research Protections, 11/05/2004 University of Southern California - Health Science/Charles R. Drew University, Available at: http://www.hhs.gov/ohrp/detrm_letrs/YR04/nov04c.pdf. The determination letter was for Human Research Subject Protections Under Federalwide Assurance (FWA) 5906 and FWA 2736. Recipients of the letter were Cornelius W. Sullivan, Ph.D., Vice Provost for Research, University of Southern California - Health Science, 300 Bovard - University Park Campus, Los Angeles, CA, and Harry E. Douglas, III, D.P.A., Interim President, Charles R. Drew University, School of Medicine and Science, 1731 East 120th Street, Los Angeles, CA.

475 OHRP, Available at: http://ohrp.osophs.dhhs.gov/detrm_letrs/lindex.htm.

476 42 C.F.R. § 93.210 Good faith as applied to a complainant or witness, means having a belief in the truth of one's allegation or testimony that a reasonable person in the complainant's or witness's position could have based on the information known to the complainant or witness at the time. An allegation or cooperation with a research misconduct proceeding is not in good faith if made with knowing or reckless disregard for information that would negate the allegation or testimony.

477 42 CFR part 50, subpart A, ''Responsibilities of Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science,'' has been replaced by 42 CFR part 93, ''Public Health Service Policies on Research Misconduct.''

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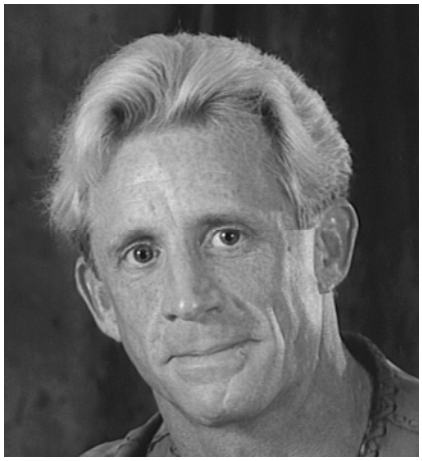
480 This includes the failure to use sound research design and which do not unnecessarily expose subjects to risk, failure to ensure that the risks to the subjects are reasonable in relation to the anticipated benefits, and failure to ensure that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

481 Informed consent deficiencies includes the failure to document accurately the duration of subject's participation, failure to document the foreseeable risks or discomforts to the subject, failure to document risks greater than minimal risk that include failure to explain medical treatments for injury, failure to document risks of particular treatment to the subject, failure to document treatment costs for injury from treatment, failure to document consequences of withdrawal from research, and failure to provide subjects with information and findings that relate to the subject's willingness to continue participation.



Dr. Scally's education includes a double degree major in Chemistry (1975) and Life Sciences (1975) from the Massachusetts Institute of Technology (M.I.T.) Cambridge, MA. Following, from 1975-1980, in the M.I.T. Division of Brain Sciences & Neuroendocrinology Dr. Scally researched and published investigations on neurotransmitter relationships. Dr. Scally's research included involvement and participation in the earliest studies detailing the role of tryptophan, serotonin, and depression. During this time, he entered the prestigious Health Sciences & Technology Program, a collaboration of M.I.T. and Harvard Medical School. In June 1980, Dr. Scally was awarded by Harvard Medical School a Doctorate of Medicine, M.D. Continuing his education, Dr. Scally continued his medical training at Parkland Memorial Hospital, Southwestern Medical School.

The medical community holds that the hypogonadism does not occur after stopping prescription androgens and is not a medical concern. The accepted standard of care within the medical community is to do nothing. This is proving to not be the case and now jeopardizes the health and welfare of countless individuals. Dr. Scally's research and investigations early on recognized the lack treatment for individuals using androgens after their cessation, both licit and illicit. Dr. Scally has personally cared for thousands of individuals using androgens. His concerns and treatments for the period after androgen cessation has been presented before the Endocrine Society, American Association of Clinical Endocrinologists, American College of Sports Medicine, and the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, as well as the focus of now published peer-reviewed literature.

In this book, Dr. Scally exposes the ethical, legal, and medical violations in androgen research. After reading the book, one is awestruck that medical research continues that violates the most basic and fundamental human rights. That this is possible is easily be attributable to pharmaceutical industry funding, governmental ignorance, and medical community complicity. Hopefully, this research will find correction sooner rather than later. Dr. Scally maintains a website on androgen use, including administration and cessation, located at http://www.asih.net.

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