

AMERICA'S NUREMBERG:

**Human
Experimentation
in
Anabolic
Steroid
Research**

**AMERICA'S NUREMBERG:
HUMAN EXPERIMENTATION IN
ANABOLIC STEROID RESEARCH**

**The Ethical, Medical, & Legal Violations
of Human Research Protections in
Anabolic Steroid Research**

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ABOUT THE AUTHOR

In this book, Dr. Scally exposes the ethical, legal, and medical violations in androgen research. The book demonstrates in a clear, detailed, and methodical analysis the ethical principles, medical foundation, and the legal and regulatory framework of clinical care. After reading the book, one is awestruck that medical research continues that violates the most basic and fundamental human rights. That this is possible might more easily be due to the foresight and intelligence of Dr. Scally rather than pharmaceutical industry funding, governmental ignorance, and medical community complicity. Dr. Scally's background lends a strong credibility to the former. Throughout the career of Dr. Scally, there are hallmarks of leadership, firsts, discovery, and pioneering events.

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.¹ 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 manage

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.

As a competitive athlete, Dr. Scally was the second-place finalist in the 1994 Mr. Texas Bodybuilding Championship at the age of 42. This brought him into contact with illicit AAS users requesting medical assistance on AAS cessation. The published literature reports include the common occurrence of hypogonadism after AAS cessation but with no treatment available. At the same time the Internet became widely available, testosterone prescribing for ageing increased exponentially, the watershed publication of testosterone and muscle mass and strength appeared in 1996, and the prescribing of anabolic steroids for various muscle wasting conditions began to rise. The paradox of AAS prescribing for increasing muscle mass and strength but without the recognition for the adverse effects of loss of muscle mass and strength, increased adiposity, and mood disturbances after AAS cessation was both troublesome and a concern to Dr. Scally.

In 1996, 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).

Within a short time, 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. 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.² Consistent with the AMA Code of Ethics, Scally discussed and published his findings in peer reviewed medical literature.³

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.⁴

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.⁵ He remains as the sole physician by reputation and publication to actively pursue and advocate the proper use of AAS to optimize health. Numerous peer-reviewed publications have come to prove the concerns and warnings. This book is yet another example of Dr. Scally's ability and talent to foresee, anticipate, and act on medical concerns for the greater public health & welfare. Dr. Scally maintains a website on androgen use, including administration and cessation, located at <http://www.asih.net>.

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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 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.

The anabolic 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 negate and 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.

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. Additionally, the failure of any action promotes and encourages the illicit use of anabolic steroids.

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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.

"The right to search for truth implies also a duty: one must not conceal any part of what one has recognized to be true." Albert Einstein

AMERICA'S NUREMBERG: HUMAN EXPERIMENTATION IN ANABOLIC STEROID RESEARCH is a discussion of the ethical, medical, and legal violations for human subject protections in anabolic steroid research. Included are forces that undermine the barriers and serve to create conditions for human research abuse. The final arbiter of whether abuse occurs falls squarely upon the physician scientist. It is only by the research design and consent of the physician investigator does human experimentation ultimately takes place. The book describes how the ongoing public health and welfare is in danger due to government ignorance, pharmaceutical industry funding, and medical research community complicity. The money involved easily exceeds hundreds of millions of dollars. Those individuals affected number into the hundreds of thousands. The intended audience for this book series is both layperson and professional, alike.

AMERICA'S NUREMBERG: HUMAN EXPERIMENTATION IN ANABOLIC STEROID RESEARCH is a chronicle of current day human research abuses. Clinical application of published study results is dependent upon sound research design. Anabolic 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 hypogonadism 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.

In many chronic illnesses, we can now achieve disease stability but not cure. In these chronic disorders, loss of muscle occurs frequently and is associated with debility, impaired quality of life, and poor disease outcome. Similarly, as men grow older, their muscle mass decreases and fat mass increases in association with a decline in testosterone levels. Therefore, strategies that can reverse muscle wasting and augment muscle function may reduce the burden of disease, improve quality of life, and reduce utilization of health care resources.

For decades, AAS administration to increase muscle mass and muscle strength has been a fact amongst illicit, black-market, users. Despite the obvious changes in musculature and appearance to even the most uninitiated the academic community steadfastly refused to admit to any association. After decades of declarations by so-called pundits that use of anabolic steroids does not affect muscle mass and muscle strength, scientific evidence shows the contrary to be true. In 1996, Bhasin et al. reported testosterone administration causes an increase in muscle mass and muscle strength.¹ Anabolic steroids increase muscle mass and muscle strength. Thus, the evolution of AAS treatments for their ability to increase muscle mass and improve muscle strength.

Anabolic steroids (AAS) previously thought to be only a concern of illicit users is now commonly a prescribed drug. The current prescribing of AAS, including testosterone, is for sarcopenia (loss of muscle mass and muscle strength with ageing), chronic kidney disease (hemodialysis), HIV+ males, chronic obstructive pulmonary disease (COPD), osteoporosis, and long-term glucocorticoid treatment. Consider the following real life scenarios.

An elderly man, 65+ years, is receiving a prescription anabolic steroid (oxymetholone or oxandrolone) to improve his appetite, muscle mass, and muscle strength.

A patient with chronic kidney disease on hemodialysis is receiving a prescription anabolic steroid, nandrolone decanoate, to improve their nutritional status and blood cell count (hemoglobin and hematocrit).

An HIV+ male previously prescribed human Growth Hormone (rhGH) for weight gain, has his prescription changed to an anabolic steroid, nandrolone decanoate,

by the attending physician based on a published clinical trial concluding that it is superior to the FDA approved rhGH.

A middle-aged man, to counteract the long-term effects of glucocorticoid (prednisone) therapy for a rheumatological disease, is taking the prescription anabolic steroid nandrolone decanoate.

A patient with COPD associated weight loss is receiving a prescribed anabolic steroid, oxandrolone, to facilitate weight restoration.

A 50 year-old male diagnosed with PADAM (andropause), prescribed testosterone for three years, is now unable to discontinue the prescription due to the adverse effects of depression, cognitive impairment, and decrease libido.

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. While the anecdotal and research reports of AAS benefits are inarguable, there are definitely inherent dangers with this class of medicines. The gravest danger and one found in the published literature for over fifty years is the period after their cessation. This period is termed anabolic steroid induced hypogonadism (ASIH). ASIH occurs in one-hundred percent of individuals administered AAS. The variables are the duration and severity of ASIH.

ASIH has adverse consequences that negate or eliminate the primary outcomes in most published studies. Earlier studies demonstrate the improvements in body composition obtained during AAS administration, after AAS cessation a reversal and loss of gains occurs. The conclusion from induced hypogonadism is loss of muscle mass, decreased muscle strength, and increased adiposity. Studies advocating AAS administration for their positive body composition changes fail to consider the period after their cessation in which these positive changes completely or almost entirely disappear.

There is the additional problem, often very serious and life threatening, of the associated signs and symptoms of hypogonadism that occur after AAS cessation. Just as athletes knew that anabolic steroid use increases muscle mass and muscle strength, they also know that cessation of anabolic steroid use causes a loss of muscle mass and muscle strength as well as a host of other problems. Upon AAS cessation, psychological disturbances include aggressiveness, depression, anxiousness, potency problems

(libido), sleep disorders, and mood disturbances.² Other adverse events occur during this period of induced hypogonadism, notably an increase in cardiovascular risk. In 2007, peer-reviewed literature concludes the use of induced hypogonadism is associated with earlier onset of fatal myocardial infarctions compared with men not treated with induced hypogonadism.³

A teenager taking illicit AAS to gain muscle mass, discontinues the AAS only to suffer from severe depression, and despite antidepressant treatment commits suicide.

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 entitled, "Restoring Faith in America's Pastime: Evaluating Major League Baseball's Efforts to Eradicate Steroid Use."⁴ 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."⁵

The Government Reform Committee received testimony from Mr. Raymond and Dr. Denise Garibaldi, parents of former USC baseball player, Rob Garibaldi, who committed suicide after stopping steroid use at the age of 24; 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 AAS cessation at the age of 17, and from Kirk J. Brower, M.D., University of Michigan, who states, "[d]epressive episodes and suicide attempts are most likely to occur within three months of stopping AAS use." After the cessation of anabolic steroids (AAS), a period of hypogonadism ensues, an adverse event. The name for the condition during this period is anabolic steroid induced hypogonadism (ASIH).

The entire history of AAS is a refusal of the medical and academic community to the realities of AAS in order to align itself with the political climate of the day. Rather than research the obvious AAS effects, the medical and academic community took what was and is the political chosen path. The medical and academic community was wrong and continues to be wrong.

Historically, the difference in the beliefs held by the athletic and the physician/academic communities on AAS are contradictory and irreconcilable. The bases of the athletes' opinions are on direct observational material. In contrast, the physician/academic communities' bases for their opinions are political in nature, self-serving, and absent support from the scientific literature. It is no surprise, then, that

peer-reviewed literature proves the athletic community has been correct on each and every issue concerning AAS, while the physician/academic communities is wrong, completely and entirely. These beliefs include the following:

Athletes held AAS increase muscle mass, muscle strength, and athletic performance. Physicians held that only replacement doses of testosterone when given to hypogonadal men and prepubertal boys have anabolic effects. According to physicians, supraphysiological doses of testosterone do not cause a further increase in muscle mass. Research demonstrates replacement doses of testosterone when administered to hypogonadal men and supraphysiological doses when administered to eugonadal men increase fat-free mass, muscle size, and muscle strength.

Athletes held higher doses of AAS promote greater increases in muscle mass and muscle strength than lower doses. Physicians held beyond the physiologic range, further increases in the dose of AAS would produce no further gains in fat-free mass and muscle strength. Research demonstrates a linear dose–response relationship exists between testosterone dose and its anabolic effects over a wide range of concentrations extending from subphysiologic to supraphysiologic range.

Athletes held the anabolic and androgenic activities of AAS could be dissociated, so that some derivatives of testosterone have preferentially greater anabolic activity than androgenic activity. Physicians held the anabolic and androgenic activity could not be dissociated and they are described by the same dose–response relationship. Research demonstrates different androgen-dependent processes have different dose response relationships.

Athletes hold the effects of AAS administration cause an up-regulation of the skeletal muscle androgen receptor (AR). Physicians hold the effects of AAS administration cause a down-regulation of the skeletal muscle androgen receptor (AR). Research demonstrates AAS administration causes an upregulation of the skeletal muscle and bone androgen receptor (AR).

Until now, with the exception of illicit AAS users, the results of these invalid and false beliefs held by the physician/academic communities did not equate to adverse consequences to the public health and welfare. This has changed with the widespread prescribing of AAS for chronic illnesses. Published literature reveals harm to individuals as well as probable and potential harm for thousands of others receiving prescription AAS. Currently held beliefs, falsely, by the medical community place the public health and welfare in danger.

Athletes hold signs & symptoms after AAS cessation are due to inadequate gonadal function. Physicians hold AAS use is associated with adverse health consequences that include chemical dependency/addiction. According to physicians, signs and symptoms after AAS cessation are indications of AAS withdrawal and AAS dependency. There is no medical or scientific literature that supports AAS dependency/addiction. AAS dependency/addiction is not a recognized disease within the ICD-10 or the DSM-IV. The ICD-10 is the official classification of diseases by the World Health Organization (WHO) used throughout the world. The DSM-IV (Diagnostic & Statistical Manual) compiled by the American Psychiatric Association, is the legally recognized list of psychiatric disorders.

Athletes hold HPTA normalization, return of normal function, after AAS cessation is variable, and sometimes may never occur. Physicians hold AAS cessation uniformly results in the return of normal function with the period after AAS cessation of no physiological consequence. Research demonstrates ASIH ensues for both illicit and licit AAS use after AAS cessation with the severity and duration unknown.

The former is discussed in a book addendum but it is the latter that is the focus of this book. 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:⁶

"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.

Anabolic 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 steroid cessation to the detriment of the public health and welfare.

In the *Structure of Scientific Revolutions*, Kuhn argued that the central concept in any science is that of "normal science" or the prevailing "paradigm."⁷ A "paradigm," according to Kuhn, is the prevailing combination of theory, standards, and acceptable methods of investigation and confirmation in a scientific community. Crucial to the notion of a paradigm is the view that from time to time, anomalous observations occur that do not seem to fit easily into the prevailing paradigm. When this occurs, there may be modification of the paradigm to accommodate the anomalous observation without having to abandon the paradigm altogether.

Kuhn suggested scientific revolutions occur because sometimes the anomalies pile up to such an extent that it is almost impossible to adjust the prevailing paradigm in a reasonable manner that takes account of the anomalies. Eventually, someone proposes a new paradigm that supplants the existing one by accounting not only for all the phenomena explained without flaw by the older paradigm, but also for all those phenomena that were anomalous under the old paradigm.

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.

The Declaration of Geneva obliges a doctor to "practise my profession with conscience and dignity."⁸ "A physician shall, in all types of medical practice, be dedicated to providing competent medical service in full technical and moral independence, with compassion and respect for human dignity. . . . A physician . . . shall strive to expose those physicians deficient in character or competence, who engage in fraud or deception."⁹

The steps and hurdles a researcher must take to publish and advocate a treatment with a basis in unsound research design and unsound scientific methodology is many. First, basic ethical principles should stop most scientists from designing and testing hypotheses that hide or limit the truth. Second, there is the presence of written codes and declarations to prevent such practices. Third, ethical principles, codes, and declarations have little, if any, legal force. Therefore, regulations and laws would seem to halt the use of unsound research involving even the remote chance of human research subject abuse. Despite these hurdles, questionable research practice and scientific misconduct, many with their foundation in conflicts of interest, continue to cause human research abuses. This book describes these hurdles, yet as the story is told too many times these are not enough to prevent human research abuse.

Research involving human participants raises ethical concerns because individuals may experience risks and inconveniences primarily to benefit others by advancing scientific knowledge. The human research subject has been fraught with danger and suffering. Advances in protection for human subjects have often come in response to particular abuses or scandals. History has shown that human research should occur only under the strictest of guidelines. Accounts of unethical human experimentation date as far back as Hippocrates and Ptolemy.¹⁰ Time again has shown examples of a patient's best interest falling to the wayside for the goals of others. Within the past decade, there have been repeated instances of deaths in human research subjects.

In 1996, 19-year old Hoiyan Nicole Wan dies from a fatal dose of lidocaine while participating in a M.I.T. sponsored medical research project at the University of Rochester Medical Center.

In 1999, 18-year-old Jesse Gelsinger dies after being injected adenovirus in a gene therapy experiment at the Institute for Human Gene Therapy at the University of Pennsylvania. After a Congressional Hearing and an FDA investigation, the principal investigators were suspended from conducting human research. The principal investigators and the University both owned shares in Genovo, a company that stood to benefit if the research were successful.

In 2001, 24 year-old healthy volunteer Ellen Roche dies after inhaling hexamethonium in an asthma study at Johns Hopkins Medical Center.

In 2001, Elaine Holden-Able, a healthy retired nurse, dies in Case Western University Alzheimer's experiment after ingesting a fatal dose of a dietary supplement. Investigators later found 10 times the normal dose of methionine in Holden-Able's blood.

In 2001, Maryland's highest court issued a scathing indictment of a study run by an affiliate of Johns Hopkins University.¹¹ The study conducted by the Kennedy Krieger Institute explored the effectiveness of different levels of lead abatement in low-income housing in Baltimore on lead uptake in young children.

In 2004, 19 year-old healthy volunteer Traci Johnson commits suicide while a subject in Eli Lilly experiment on antidepressant medication.

In 2004, the BBC documentary "Guinea Pig Kids" and BBC News article of the same name, reporter Jamie Doran reveals that children involved in the New York City foster care system were unwitting human subjects in experimental AIDS drug trials from 1988 onward.

However, the gauge of human research abuses is not measured by deaths. Human research abuses occur most often under conditions termed as under the radar. An adverse event (AE) is any experience or abnormal finding that has taken place during the course of a research project and the AE was harmful to the subject participating in the research, increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio. An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory value, symptom, or disease

temporally associated with the use of a test treatment, whether or not related to the test treatment.

The subordination of human subject protections to "the interests of science and society" may lead to a proliferation of greater than minimal risk investigations (frequently mislabeled as minimal risk), carried out without consent or with flawed consent procedures, and in some cases to harm that might have been avoided.¹² A willingness to dilute protections for human subjects and a failure to respect individual autonomy in the research setting is likely to have a marked effect on the clinical setting as well.¹³

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.¹⁴ The well-intentioned and caring physician may place an individual on published clinical treatments that use questionable research practices and scientific misconduct.

Jay Katz comments,¹⁵ "I believe that the concentration camp experiments, which transgressed the last vestiges of human decency, can be located at one end of a continuum, but I also believe that toward the opposite end, we must confront a question still relevant in today's world: How much harm can be inflicted on human subjects of research for the sake of medical progress and national survival?" "Doubling," however, is an all too human phenomenon. Indeed, it is a ubiquitous manifestation of man's conflictual nature. And physician-investigators are particularly susceptible to the perils of doubling. In their scientific pursuits, doctors are double agents, because their commitment to the objective imperatives of the research protocol conflicts with, and can take precedence over, the individual needs of patients. Thus, in human research, the healing-harming-(killing) "paradox" is inherent in the task itself."

The primary responsibility as a physician is the diagnosis and treatment of an individual. To this end, a physician must bring forward all of their training, skill, education, experience, and knowledge. Should harm come in the direction of an individual the last person to prevent the occurrence is their physician. It is with this responsibility and trust that a physician is free of any and all undue influence that would diminish their vigilance to guard and protect one's health.

The healthcare of the individual is in a delicate balance of forces between rights articulated in ethical codes and declarations, protections found in regulations and laws, and dangers finding expression in conflicts of interest, questionable research practices, and scientific misconduct.

One is easily convinced that conflicts will always resolve themselves in favor of patients. The human capacity for self-deception needs to be recognized and we must accept that none of us is immune from its insidious expression. Doing the best for patients requires that they trust us absolutely to act always in their best interest.¹⁶ For physicians, the challenge is to articulate and follow a universal medical ethics, based on human rights, and to guard this ethic, for the sake of humanity, against its subversion and corruption by governments and corporations that would use medicine for its own purposes.¹⁷

The Nuremberg Doctors' Trial should teach us three very important lessons: (1) Statements, even authoritative statements, of medical ethics are not self-enforcing and require active promulgating, education, and enforcement; (2) human experimentation and torture are important areas where violations of human rights and medical practice occur, but are too narrow in themselves to provide guidance for physicians and the public on the broad range of physician involvement in human rights abuses around the world; and (3) there is no effective mechanism to promulgate and enforce basic medical ethics and human rights principles in the world, and there should be.

PART 1

The canary in the coalmine is an expression for a warning of impending disaster so that others might flee and avoid harm. The interpretation can also be a warning so that one takes appropriate action for the prevention or minimization of a disaster. Thus, the physician-scientist has a canary in the coalmine in the form of ethics, codes, and laws that die before embarking upon research that is unsound or invalid. Human research subject abuses do not suddenly appear but are present within the published literature years before discovery, if, at all, by the wider medical community or public. Many answer for their transgressions, but only if others that recognize the failings are able to bring a public outcry, halt, or change by authorities in the power to do so.

Part 1 includes the history, development, and implementation of the ethical, medical, and legal framework found in codes, declarations, regulations, and laws. These serve as guideposts and constraints for the physician-scientist. Chapter 1 serves to guide the individual on what is right or wrong, good and evil, articulated in oaths, codes, and declarations. Science, Chapter 2, is amoral, has as a basis the scientific

method, and serves the progress in society. Despite the mandates of oaths, codes, and declarations, however, the application of science in the wrong hands can be destructive. History shows that some physicians use their knowledge and position to harm patients, often under the umbrella of medical research, Chapter 3. The most notorious of these cases occurred by the Nazis during World War II. To guide its verdicts in the Nuremberg Doctors Trial in 1947, the court issued the Nuremberg Code, shortly followed by other declarations and codes articulating universal human rights, Chapter 4. The mere writing of human rights has little legal force, if any, and human research subject abuses led to the passage of laws, 45 C.F.R. 46, commonly referred to the Common Rule, Chapter 5, and the provisions for informed consent, Chapter 6, and the institutional review board, Chapter 7. Despite the codification of human research subject protections, there was the necessity for the establishment of governmental agencies, Office of Human Research Protection (OHRP) and Office of Research Integrity (ORI), to assure compliance with federal regulations and the integrity of scientific research, Chapter 8. The location of evidence, evidence based medicine, is within the peer-reviewed literature, Chapter 9, although it is necessary to be aware of forces, conflicts of interest and scientific misconduct, which subvert this evidence, Chapter 10.

CHAPTER 1 - ETHICS

"The issue of patient protection is, at its very root, an ethical question--not simply a legal or scientific question."¹⁸ Ethics, or moral philosophy, is concerned with the study of values, that is, of morals and morality. It is devoted to systematizing, defending, and recommending concepts of right and wrong behaviour by analyzing concepts such as right, wrong, good, and evil.

The Oath of Hippocrates is considered the first code written in an organized and logical way that describes the proper relationships between physician and patient. The Hippocratic Oath established the physician's duty to the patient. The first sentence of the Oath is simple, yet straightforward: "Above all, do no harm." The Oath further states, "I will use my power to help the sick to the best of my ability and judgment; I will abstain from harming or wrongdoing any man by it." Today, the Oath provides a foundation for medical ethics. It sets forth the physician's duty to work in the best interest of the patient, and to avoid harming, or suggesting treatments that will harm, the patient. This is the basis for the American Medical Association "Code of Medical Ethics" issued in 1847. Medical ethics in the modern sense refers to the application of general and fundamental ethical principles to clinical practice situations, including medical research.

CHAPTER 2 - SCIENCE

Science has long held a privileged status in society. Science helps explain why things are as they are or are not. Science can be many things, but its use is often a source of legitimation or apologetics, to prove what people already believe to be true. Science is a powerful tool and people look to it for solutions. Science is amoral. However, the application of science in the wrong hands, science can serve as a powerful destructive force, causing morbidity and mortality in its application.

CHAPTER 3 - HUMAN RESEARCH ABUSES

In medicine, medical ethics begins and ends in the patient–physician relationship. The conception we hold of that relationship shapes the decisions we make in every clinical situation. It sets the standard for right and wrong, good and bad, professional conduct. It is the final arbiter of the moral status of every policy affecting the health of individuals or the public. How we see that relationship will determine the kind of society we are, have become, or want to be.¹⁹

In 1865, French physiologist Claude Bernard publishes "Introduction to the Study of Human Experimentation," advising: "Never perform an experiment which might be harmful to the patient even though highly advantageous to science or the health of others." When science takes man [sic] as its subject, tensions arise between two values basic to Western society: freedom of scientific inquiry and protection of individual inviolability.²⁰ These tensions historically reveal themselves in human research abuses.

CHAPTER 4 –NUREMBERG

Human research abuses exposed as war crimes following World War II resulted in the Nuremberg Code. The Nuremberg Code of 1947 "[r]emains the most authoritative legal and ethical document governing international research standards and one of the premier human rights documents in world history."²¹ The Nuremberg Code includes such principles as informed consent and absence of coercion, properly formulated scientific experimentation, and beneficence towards experiment participants.

In 1948, the Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations and the World Medical Assembly adopted an International Code of Professional Ethics - Declaration of Geneva. In June 1964, the World Medical Association (WMA) adopted the Declaration of Helsinki - Principles for Those in Research and Experimentation. The Declaration of Helsinki states "concern for the interests of the subject must always prevail over the interests of science and society." These codes and declarations set the stage for what is later to become law.

CHAPTER 5 - 45 C.F.R. § 46: "THE COMMON RULE"

The Nuremberg Code and the Declaration of Helsinki form the basis for current United States regulations on human research protections. The National Research Act in 1974 established the "National Commission for Protection of Human Subjects of Biomedical and Behavioral Research," which published the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research) in 1979 and laid the foundation for the primary research principles of beneficence, justice, and respect for persons. Also in 1974, saw the first publication of 44 C.F.R. § 46, Subpart A by the Department of Health and Human Services (DHHS). In 1991, 44 C.F.R. § 46, Subpart A was adopted by 16 federal agencies, and thus became known as the Common Rule. 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.

CHAPTER 6 - INFORMED CONSENT

Informed consent is a codified regulation of the Common Rule. The principle of voluntary informed consent protects the right of the individual to control his own body. Informed consent process applied to research involving human subjects is a human rights issue, and is based on the fundamental principle of "respect for others." 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.

CHAPTER 7 - INSTITUTIONAL REVIEW BOARD (IRB)

The Public Health Service Act mandates that DHHS develop and implement a program to obtain advance assurances from institutions that they will establish an institutional review board (IRB) to protect the rights and welfare of the human subjects. An IRB is a formally designated group to provide compliance oversight (approve, monitor, and review) and guidance on ethical issues in biomedical or behavioral research. The primary focus of the IRB review is on the safety and well-being of research participants. This includes the approval of the study research design and informed consent. An institution's assurance must designate the IRB applicable to a given research protocol, include a written list of the IRB's members, and describe the procedures that the IRB will follow in discharging its duties.

CHAPTER 8 - OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP) &

OFFICE FOR RESEARCH INTEGRITY (ORI)

The federal Office for Human Research Protection (OHRP) is the primary government agency responsible for enforcing the federal human subject protection regulations, known as the Common Rule. OHRP issues a federalwide assurance, a legally binding document that commits an institution to complying with federal standards for the protection of human subjects in clinical trials. These include the use of sound research design, sound research methodology, and informed consent. The Office of Research Integrity (ORI) promotes integrity in biomedical and behavioral research supported by the U.S. Public Health Service (PHS) and monitors institutional investigations of research misconduct.

CHAPTER 9 - EVIDENCE BASED MEDICINE

Evidence based medicine (EBM) is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. EBM seeks to clarify those parts of medical practice, which are in principle subject to scientific methods, and to apply these methods to ensure the best prediction of outcomes in medical treatment.

The first element, individual clinical expertise, is judgment and clinical skills obtained from clinical experience and practice. The second element of evidence-based medicine, the best available medical evidence, is what differentiates evidence-based medicine from what has been referred to as "eminence-based medicine."²² It includes the concept that the practice of medicine bases be on firm data rather than anecdote, tradition, intuition, or belief.

Practicing evidence-based medicine implies not only clinical expertise, but also expertise in retrieving, interpreting, and applying the results of scientific studies, and in communicating the risks and benefit of different courses of action to patients. To effectively apply evidence in practice, in addition to skills in taking a history, conducting an examination, determining a diagnosis, and determining appropriate options for intervention, a clinician must have the ability to: (1) identify gaps in knowledge, (2) formulate clinically relevant questions; (3) conduct an efficient literature search; (4) apply rules of evidence, including a hierarchy of evidence, to determine the validity of studies; (5) apply the literature findings appropriately to the patient problem; and (6) understand how the patient's values affect the balance between potential advantages and disadvantages of the available management options, and appropriately involve the patient in the decision.²³

CHAPTER 10 - CONFLICTS OF INTEREST & SCIENTIFIC MISCONDUCT

Conflict of interest is, "A conflict between the private interests and official responsibilities of a person in a position of trust."²⁴ The spectrum of scientific conduct is varied. Investigators who perform research that is free from bias and error are contributing to objective science. Investigators whose work has been marred by unintentional bias or error practice imperfect science. 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."²⁵

PART 2

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.

Chapter 11, 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. Chapter 12 provides a background on testosterone and related analogues, anabolic steroids. Chapter 13, 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 14. Vulnerable populations exposed to AAS administration with no consideration for the period after AAS cessation include human immunodeficiency virus (HIV), Chapter 15; chronic obstructive pulmonary disease (COPD), Chapter 16; chronic kidney disease: hemodialysis, Chapter 17; osteoporosis & glucocorticoids, Chapter 18, and sarcopenia, Chapter 19. Lastly, Chapter 20 reveals the governmental ignorance, institutional complicity, and investigator doublethink in defense of unsound research design, unsound research methodology, and improper informed consent.

CHAPTER 11 - 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 12 - 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 stanozolol.

CHAPTER 13 - 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 14 - HYPOGONADISM & ANABOLIC STEROID INDUCED HYPOGONADISM (ASIH)

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 15 - 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 16 - 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 17 - 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 18 - 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 19 - 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 20 – 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.²⁶ 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.

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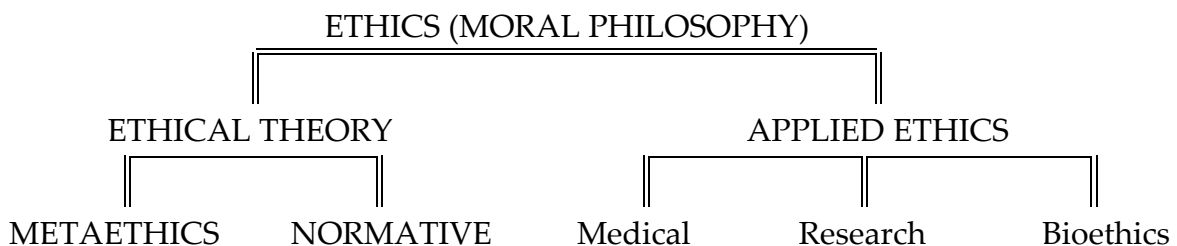
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ETHICS

"Reading about ethics is about as likely to improve one's behavior as reading about sports is to make one into an athlete." Mason Cooley

Political discourse has shown great sensitivity to ethical issues. This heightened sensitivity to ethical issues is a welcome change from the power politics that dominated discussions during the post-World War II period. The imperatives of Realpolitik¹ previously forced ethical considerations to be secondary. Ethics of care have come to the fore. Nevertheless, the mere use of ethical language does not necessarily mean there is clarity of ethical thought.² Ethics (from the Ancient Greek 'ethikos,' meaning 'arising from habit'), or moral philosophy, is concerned with the study of values, that is, of morals and morality. It is devoted to systematizing, defending, and recommending concepts of right and wrong behaviour by analyzing concepts such as right, wrong, good, and evil.

Ethical divisions are into three primary areas: metaethics, normative (or prescriptive) ethics, and applied ethics.³ Metaethics is the study of the origin and meaning of ethical concepts. Normative ethics is a branch of philosophical ethics concerned with classifying actions as right and wrong. Applied ethics is the application of normative theories to practical moral problems.



SCIENCE

"Science is facts. Just as houses are made of stones, so is science made of facts. But a pile of stones is not a house and a collection of facts is not necessarily science." Jules Henri Poincaré

"Science may be described as the art of systematic over-simplification." Karl Popper

Science is from the Latin word, *scientia*, to know. Science is the investigation of natural phenomena through observation, theoretical explanation, and experimentation, or the knowledge produced by such investigation. Science is an objective, logical, and repeatable attempt to understand the principles and forces operating in the natural universe. There is no right and wrong, only correct and incorrect. Science is amoral.

Today, few would deny the central importance of science to our lives, but not many would be able to give a good account of what science is. To most, the word probably brings to mind not science itself, but the fruits of science, the pervasive complex of technology that has transformed all of our lives. However, science might also be thought to include the vast body of knowledge we have accumulated about the natural world. There are still mysteries, and there always will be mysteries, but the fact is that, largely, we understand how nature works.¹

There are some questions solved by logical argumentation² and other questions by empirical observation.³ Mathematics proceeds through steps of logical argumentation. There are limitations, however, to inquiring about the world merely through logical argumentation. The observations on the relationships in nature necessarily require a different form of proof. Methods to explain the workings of nature require and demand proof by experimental confirmation. A new method, empirical observation, of acquiring knowledge was becoming common and showing results.

The most striking contemporary articulation of this new method of inquiry was by Sir Francis Bacon (1561-1626), the Lord Chancellor of England, in *Novum Organum*.⁴

HUMAN RESEARCH ABUSE

"When science takes man [sic] as its subject, tensions arise between two values basic to Western society: freedom of scientific inquiry and protection of individual inviolability."¹ Jay Katz

"Science, unguided by a higher abstract principle, freely hands over its secrets to a vastly developed and commercially inspired technology, and the latter, even less restrained by a supreme culture saving principle, with the means of science creates all the instruments of power demanded from it by the organization of Might." Johan Huizinga

Medicine is the maintenance of health and the prevention, alleviation, or cure of disease. Medicine is the science and ethics of care. Science and ethics are the two pillars of medicine, with medicine deriving support from each. Caduceus portrays science and ethics in a more complex, intertwined relationship, as the snakes that twist around the staff. Regardless of the image, the essential principle is that science should serve the cause of medicine rather than humans serving the cause of science. Ethics differs from science. The most widely used terms in ethics are "good or bad," "proper or improper," and "correct or incorrect." In contrast, in the sciences the terms used are "true and false."

In *On the Origin of Species by Means of Natural Selection* (1859), Charles Darwin outlined a biological theory about how new species are formed and existing ones become extinct.² After its publication, many anthropologists and scientists sought to apply this theory to humans. Known as social Darwinists, they explained human society in terms of natural selection, presumably inspired by Darwin's candor:³ The American eugenics movement at the turn of the past century was built on what was considered cutting-edge scientific knowledge from Darwinian evolution and Mendelian genetics.⁴ Based on flawed and simplistic science, it adversely affected the lives of tens of thousands of persons in the United States and elsewhere.⁵

NUREMBERG

The Nuremberg Code of 1947 “[r]emains the most authoritative legal and ethical document governing international research standards and one of the premier human rights documents in world history.” George J. Annas

"As medical professionals, we remain unconvinced that we should embrace the code's principles in the spirit in which they were promulgated. It remains my dream that we shall do so. It may only be a dream, but it comforts my nightmares."¹ Jay Katz

Bioethicists George Annas and Michael Grodin have called the trials of the Nazi physicians “the most important historical forum [ever] for questioning the permissible limits of human experimentation.” The second Nuremberg Trial, the Doctors' Trial, concluded on August 19, 1947. As part of the final judgment of the 1946-1947 Nuremberg Doctors' Trial, the court issued "The Nuremberg Code" as ten “basic principles” for research using human participants, now known as the Nuremberg Code.² The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects.

The first international instrument on the ethics of medical research, the Nuremberg Code, is a consequence of the atrocious experiments on unconsenting prisoners and detainees during the Second World War. The Nuremberg Code includes such principles as informed consent and absence of coercion, properly formulated scientific experimentation, and beneficence towards experiment participants.³ The principle of voluntary informed consent protects the right of the individual to control his own body. This code also recognizes that the weighing of risk against the expected benefit, and the avoiding of unnecessary pain and suffering. This code recognizes that doctors should avoid actions that injure human patients.

There are many recorded instances of unethical human experimentation. There is also a history of crimes committed and disguised as human experiments, best

45 C.F.R. § 46 "THE COMMON RULE"

"Never perform an experiment which might be harmful to the patient even though highly advantageous to science or the health of others." Claude Bernard (1865), "Introduction to the Study of Human Experimentation."

Every dose of medicine given is an experiment as it is impossible in every instance to predict what the result may be. William Osler, 1907

The National Research Act in 1974 established the "National Commission for Protection of Human Subjects of Biomedical and Behavioral Research," which published the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research) in 1979 and laid the foundation for the primary research principles of beneficence, justice, and respect for persons. Also in 1974, saw the first publication of 45 C.F.R. § 46, Subpart A by the Department of Health and Human Services (DHHS), later revised in 1979. In 1991, 45 C.F.R. § 46, Subpart A was adopted by 16 federal agencies, and thus became known as the Common Rule.¹

The Constitution of the United States sets forth the nations fundamental laws. It establishes the form of the national government and defines the rights and liberties of the American people. It also lists the aims of the government and the methods of achieving them. The 14th amendment of the U.S. Constitution is central in the protection of one's health. The following excerpt from "Brief on the Right to Essential Human Dignity"² summarizes the rights afforded by the Fourteenth Amendment. The Fourteenth Amendment provides that no State shall "deprive any person of life, liberty, or property, without due process of law." This clause "guarantees more than fair process, and the 'liberty' it protects includes more than the absence of physical restraint."³ Rights are protected under the Due Process Clause of the Fourteenth Amendment if they are "so rooted in the tradition and conscience of our people as to be ranked as fundamental" or if such rights reflect "basic values implicit in the concept of

INFORMED CONSENT

The Nuremberg Code's first principle, "The voluntary consent of the human subject is absolutely essential," is an absolute upon which the others rest.¹ George J. Annas

The notion of consent has played a role in American research ethics and law since as far back as the 1830s,² but it was not until the Nuremberg war crime trials following World War II that consent principles were formally reduced to writing. The Nuremberg Code is the one document that seeks in uncompromising language to protect the inviolability of subjects of research.³ It deserves to be taken more seriously than it has been by the research community. It reads, "The voluntary consent of the human subject is absolutely essential." The judges went to unusual lengths to define voluntary consent, in terms of both subjects' capacity to give consent and the information that investigators must provide to subjects.

The first principle is further explained in the language which directly follows: This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

INSTITUTIONAL REVIEW BOARD (IRB)

As Carl Elliott observed about bioethicists who are hired by industry is that “they look like watchdogs but can be used like show dogs.”¹

"Relationships between IRB members and industry are common, and members sometimes participate in decisions about protocols sponsored by companies with which they have a financial relationship."²

"Another problem plaguing IRBs is “groupthink” — a phenomena in which one or more members of a group dominate the discussion, leading the group to premature closure by reaching a decision collectively which few might reach if each had relied upon his/her own critical judgment.”³

An institutional review board (IRB) is a group formally designated to approve, monitor, and review biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the subjects.⁴ Public debate reveals the need to bring fundamental ethical principles to bear on research in a formal way through federal and institutional regulations and to assure compliance with these regulations through the establishment of committees like the IRB. The development of IRBs was in direct response to research abuses earlier in the twentieth century.

In response to the atrocities committed by Nazi scientists during World War II, the Nuremberg Military Tribunal created the Nuremberg Code, a set of 10 principles for research involving human participants, including an absolute requirement for voluntary consent.⁵ The Nuremberg principles placed primary responsibility on the investigator to ensure the conducting of ethical research. At the same time that the Nuremberg Trial was proceeding, anticipating the need for a rapid response to concerns about research abuses, the American Medical Association adopted its first code of research ethics for physicians in 1946, outlining principles to follow in conducting research with human subjects.⁶

OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP) & OFFICE FOR RESEARCH INTEGRITY (ORI)

"The medical profession has been shown not to have the ability to police itself."¹
Benjamin Mason Meier

OFFICE FOR HUMAN RESEARCH PROTECTIONS

The federal Office for Human Research Protection (OHRP) is the primary government agency responsible for enforcing the federal human subject protection regulations, known as the Common Rule.² OHRP supports, strengthens, and provides leadership to the nation's system for protecting volunteers in research conducted or supported by the U.S. Department of Health and Human Services (DHHS). OHRP provides clarification and guidance on ethical issues to research institutions, develops educational programs and materials, and promotes innovative approaches to enhancing human subject protections.

Unlike its predecessor, the Office for Protection from Research Risks (OPRR), the new office charge was solely the protection of human subjects in research. The creation of OHRP was in response to a perceived crisis. That crisis was not, as many believe, simply the result of the tragic death of Jesse Gelsinger in a gene transfer experiment.³ Gelsinger's death was only the straw that broke the camel's back. It came after 20 years of largely ignored reports and recommendations calling for reform of an inefficient and questionably effective system. The Congressional hearings that followed in the wake of Gelsinger's death were a potent stimulus for long overdue reform. It reflected a growing loss of confidence in the U.S. system for human research and protection of human subjects that had evolved over more than a decade.

EVIDENCE BASED MEDICINE (EBM)

"The right to search for truth implies also a duty: one must not conceal any part of what one has recognized to be true." Albert Einstein

Evidence based medicine (EBM) is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.¹ The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. EBM seeks to clarify those parts of medical practice, which are in principle subject to scientific methods, and to apply these methods to ensure the best prediction of outcomes in medical treatment.

The first element, individual clinical expertise, is judgment and clinical skills obtained from clinical experience and practice. The second element of evidence-based medicine, the best available medical evidence, is what differentiates evidence-based medicine from what has been referred to as "eminence-based medicine."² It includes the concept that the practice of medicine bases be on firm data rather than anecdote, tradition, intuition, or belief. This is in contrast to dogma, which are those opinions held as established or put forth as authoritative or expert opinions but have little or no supportive empirical evidence from primary sources. EBM is the concept that the basis for the practice of medicine is on firm data rather than anecdote, tradition, intuition, or belief.

Practicing evidence-based medicine implies not only clinical expertise, but also expertise in retrieving, interpreting, and applying the results of scientific studies, and in communicating the risks and benefit of different courses of action to patients. To effectively apply evidence in practice, in addition to skills in taking a history, conducting an examination, determining a diagnosis, and determining appropriate

CONFLICTS OF INTEREST & SCIENTIFIC MISCONDUCT

"The problem is less conflict of interest itself; the problem is that conflict of interest may be a risk factor for scientific misconduct. . . . 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." Thomas Bodenheimer

A PubMed¹ search for the MeSH² terminology for scientific misconduct and conflict of interest produces the following definitions. Conflict of interest is a situation in which an individual might benefit personally from official or professional actions. It includes a conflict between a person's private interests and official responsibilities in a position of trust. The term is not restricted to government officials. The concept refers both to actual conflict of interest and the appearance or perception of conflict. "Conflict of Interest"[Mesh] search found 5244 citations total. These broke down by publication date from 1980 to 1989: 151, 1990 to 1999: 1808, and 2000 to 2007: 3264. Scientific Misconduct is the intentional falsification of scientific data by presentation of fraudulent, incomplete, or uncorroborated findings as scientific fact. "Scientific Misconduct"[Mesh] search found 3099 citations total. These broke down by publication date from 1980 to 1989: 275, 1990 to 1999: 1545, and 2000 to 2007: 1292.

Physicians traditionally take the Hippocratic Oath or the Oath of Maimonides upon entering the practice of medicine. The Hippocratic Oath provides, "I will follow that method of treatment which according to my ability and judgment, I consider for the benefit of my patient and abstain from whatever is harmful or mischievous." The Oath of Maimonides includes, "The eternal providence has appointed me to watch over the life and health of Thy creatures. May the love for my art actuate me at all time; may neither avarice nor miserliness, nor thirst for glory or for a great reputation engage my

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."¹ 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.²

"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."³ "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."⁴ 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."⁵

Historically, the medical profession demonstrates not to have the ability to police itself.⁶ 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

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

HYPOTHALAMIC PITUITARY TESTICULAR AXIS (HPTA)

The HPTA is a dynamic feedback loop.¹ 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

HYPOGONADISM ANABOLIC STEROID INDUCED HYPOGONADISM (ASIH)

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.

Anabolic steroid induced hypogonadism (ASIH) 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 ASIH. ASIH, as a form of hypogonadism, is a real disease with potentially serious consequences that include but are not limited to adverse body composition changes (decrease muscle mass and increased adiposity), decreased muscle strength, bone loss, increase in cardiovascular risk, adverse psychological effects (depression, low self esteem, guilt, increased stress, and anhedonia), sexual dysfunction (decreased libido, decreased spontaneous erections, decreased ejaculate, erection dysfunction, decreased sexual fantasies, and anorgasmia), decreased cognitive testing, sleep disturbances, and constitutional symptoms (general fatigue, agitation/motor dyskinesia, and decreased appetite). Reports of symptoms following use of illicit androgens also include suicidal ideation and suicide.

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

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.¹

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

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.¹ 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."² "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."³ "Treatment with Nandrolone for six months resulted in a significant increase in lean body mass associated with functional improvement in patients undergoing dialysis."⁴

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

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 70.¹ Others have confirmed that bone mineral content and bone density are negatively associated with age at most skeletal sites.²

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.³ 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.

SARCOPENIA

Sarcopenia is a word coined from Greek by Rosenberg in 1988 from *sarx* meaning flesh and *penia* meaning loss.¹ 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.² 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.³ 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.⁴

The age and sex-adjusted prevalence of sarcopenia varies from 6% to 24%, depending on the definition and measure of muscle mass used.⁵ 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.⁶ 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

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."¹

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."²

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."³ The complaint named the Departments of Medicine, Radiology, and

APPENDIX L

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."¹ 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.²

OHRP maintains a list of "compliance determination" letters on their website.³ 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.

NOTES

1 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 full text of the study appears online and is available at <http://ajpendo.physiology.org/cgi/content/full/284/1/E120>.

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.

2 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_lettrs/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.

3 OHRP, Available at: http://ohrp.osophs.dhhs.gov/detrm_lettrs/lindex.htm.

APPENDIX M

ORI RESPONSE

In August 2007, a good faith¹ 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.² 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.*"³ The following document represents the ORI response.

NOTES

1 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.

2 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."

3 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.

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.

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.

Researchers 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.

APPENDIX N

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.*"¹ The new allegations include the failure to conduct research consistent with 45 C.F.R. § 46.111.² The informed consent process for the research failed to include the elements required by DHHS regulations at 45 C.F.R. § 46.116.³ 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.

NOTES

1 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.

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2 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.

3 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.