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CHAPTER 14

Laboratory Assessment of the Paraphilias and Their Treatment with Antiandrogenic Medication

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INTRODUCTION

Recently, Wirth and Folstein of The Johns Hopkins Hospital studied a group of patients with severe kidney disease who needed to receive chronic hemodialysis maintenance care [1]. For such patients compliance with oral water and salt intake restrictions is considered essential in order to maintain optimal health. However, even though patients were repeatedly admonished by the staff to keep their weight gain between dialysis treatments at or below 0.3 kilograms per day, as shown in Figure 1, most patients failed to do so. The amount of weight gained was a function of the amount of excess fluid consumed, which in turn appeared to be a function of the degree of thirst any given patient experienced. Wirth and Folstein concluded that limits to fluid intake set by physicians may not suffice, because they differ from those set by the patients' own physiology.

When persons attempting to restrict their fluid intake or to diet state that they are unable to do so on their own, they are generally believed, and an effort

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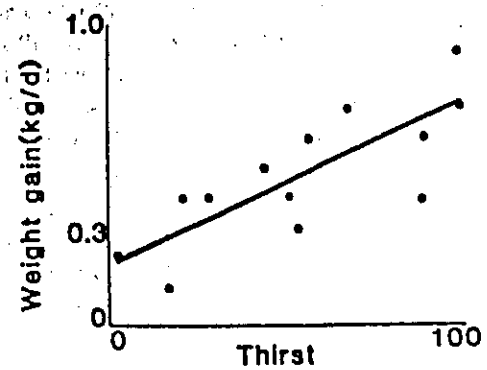

Figure 1. Water-induced weight gain as a function of self-reported thirst (as measured on a 100 mm visual analog scale) in 13 patients without kidneys on chronic renal dialysis. The requested maximum daily weight gain was 0.3 kg. The greater the thirst, the more the weight gain.

is made to provide qualified assistance to them. Similarly, when persons fail in their efforts to give up cigarette smoking, such failure is usually viewed with understanding and concern. When patients with anorexia nervosa binge-eat, or induce vomiting, it is generally accepted that they need help in order to become better able to control their own actions. The same can be said of compulsive handwashers.

On the other hand, when sexual behaviors are considered, a much different perspective is often proposed and invoked. Thus, it is usually taken for granted that "sex offenders" are invariably bad or evil people and that they could change if only they wanted to and would try their best to do so. It is possible that in some instances these assumptions may be wrong, and that instead concepts such as the medical diagnosis and treatment of "sex offenders" should be considered.

Following are verbatim excerpts from letters written by a convicted rapist. This man was found on laboratory examination to have an elevated level of follicle-stimulating hormone. He was subsequently treated with antiandrogenic medication. His example will be used as a starting point for the following discussion of the laboratory assessment and biologic treatment of "sex offenders."

> "Sir, I am 32-years-old and in the penitentiary for several rapes. All my life I've felt I wasn't normal. . . . being the sex maniac I've been . . . messed up in sexual thought and behavior for God only knows how long. Since I was 4- or 5-years-old, sex has been 90% of my thoughts. After I was married I would have sex with my wife every night, then I would go masturbate. Sex was all I could think of.
>
> The rapes started when I (saw) a naked woman through a window. Since that time its been 8 or 10, maybe more. The only way to stop the thoughts was to have sex or ejaculate. Sometimes I masturbated. After (each rape) I felt ashamed. I tried to stop and could for a month or longer, but ended up doing it again. It was as if I was being driven. I know it (doesn't) sound true or logical, but at a certain point, I could not control myself. I don't know why, if my true feelings was to be decent and good, why was I filthy and bad. I couldn't really control my mind on sexual things. The only things against the law I've ever done is because of sex. I don't like to hurt people.

Prior to antiandrogenic medication treatment, a number of paraphiliac patients have insisted that they lacked the capacity to consistently resist sexual temptations on their own. During hormone treatment, many of the same men have reported an increased capacity for self-control, and their subsequent behavior seems to confirm the validity of their assertions. This suggests that they acquired a capac[illegible] for self-control following hormonal treatment not previously present.

The compulsive rapist quoted above has now begun antiandrogenic medication treatment. He finds it helpful, as have others who have received this kind of medication. His comments about the effects of treatment, which are suggestive of a relationship between the hormone milieu of the brain and subjective mental experiences, follow.

> In here (prison) the bad things stopped. You can't do them here, but the self hate and confusion inside me did not. I was still unable to control my sexual thoughts. Then, I started the shots. The feeling I now have is a feeling I cannot express in words. I have always known right from wrong, but now I can do right when I want to. I can stop ugly thoughts from ruling my life, and I can concentrate on other things. I wish I could explain how it feels to be able to put bad thoughts aside. I could not do this before. I just can't believe the effects of the shots is (due to) psychological factors. I feel I still have psychological problems, but the control I now have in this area of my (mental) life due to the medication leads me to feel that, perhaps, some physical part of my problem was involved much more than I thought possible. If they (others) believe it or not, it ain't going to stop me from continuing to take it."

He continues receiving antiandrogenic medication treatment in prison where he is serving a life sentence.

DIAGNOSTIC INDICATIONS FOR THE USE OF ANTIANDROGENIC MEDICATIONS

A person is considered a sex offender by virtue of having behaved in a particular way—e.g., by having exposed himself publicly. However, similar behaviors

can be enacted for a variety of reasons. Not all sex offenses (a legal concept) are the reflection of a "sexual deviation disorder," or paraphilia (a medical concept).

Table 1 lists those conditions considered in DSM III to be paraphilias (sexual deviation disorders) [2]. Antiandrogenic medications are used to treat those sex offenders whose behaviors are either the expression of an unusual and troublesome sexual appetite (eg., homosexual pedophilia—a sexual appetite for young boys), or as in the case just presented, seem less than fully controllable through the application of willpower alone [3]. These two possibilities are by no means mutually exclusive. Antiandrogenic medications may have a role to play as sexual appetite suppressants in the treatment of each of the paraphilias listed in Table 1, since many such patients experience difficulty in resisting the temptation to act upon unacceptable erotic urges.

Diagnosis of a sexual deviation syndrome can be made by inquiring about a person's thoughts, feelings, and behaviors. Individuals with "deviant" sexual interests ordinarily experience repeated erotic fantasies about engaging in unconventional forms of sexual activity. Asking about masturbatory fantasies can be revealing in this respect because erotic arousal for the purpose of masturbation may be difficult in the absence of erotic mental imagery [4]. The homosexual pedophile frequently fantasizes about young boys, whereas the heterosexual exhibitionist often has recurring thoughts and urges to expose himself to women. The male transvestite is preoccupied with the idea of cross-dressing in female clothing. Measures of penile tumescence and other forms of polygraphic data have also been used to try to document unconventional sexual ideas [5], but clinically we have found this unnecessary. Usually diagnosis of a sexual deviation syndrome can be made simply by gaining the patient's confidence and asking him to describe the nature of his erotic interests and behavior.

A sex offense could represent the expression of any of a number of psychiatric conditions including schizophrenia (in which phenothiazine treatment rather

Table 1. Categories of Paraphilia ("Sexual Deviation") as Listed in DSM-III

1. Pedophilia
2. Exhibitionism
3. Transvestism
4. Voyeurism
5. Zoophilia
6. Erotic sadism
7. Erotic masochism
8. Other (numerous others, including paraphilic, or compulsive, rape)

than antiandrogens might be warranted), mania (in which lithium carbonate might prove helpful), or dementia. The use of antiandrogenic medications is not considered appropriate with all sex offenders [3].

In assessing sex offenders and to learn more about their motivations and how best to deal with them, one can ask a number of questions. What are the various states of mind which people experience that may lead them to commit a sexual offense? Is the nature of one's sexual orientation and interests to some extent independent of characterological traits (such as concern or lack of concern for others)? What environmental or biologic factors, are associated with the development of unconventional sexual interests? What happens in the brain during erotic arousal? Is it possible, through a combination of psychologic counseling and pharmacotherapy, to provide effective treatment to men who experience unconventional, or uncontrollable, sexual appetites? Some of these questions can be addressed with the aid of laboratory tests or by the application of standardized scientific methods for determining therapeutic efficacy.

The remainder of this chapter will focus primarily upon three issues. (1) What is the rationale for using laboratory tests to try to elucidate the contribution made by biologic factors to sexual appetite and behavior and what are these tests? (2) What laboratory procedures can be used to learn more about regional brain activity and how it relates to erotic arousal? (3) What is the conceptual rationale and what laboratory tests need to be employed when using antiandrogenic medications to try to treat sex offenders? Methods for performing some of the relevant tests, when to use them, how to interpret the results, and how to place them into a proper clinical perspective will also be detailed.

LABORATORY TESTS TO ASSESS FOR BIOLOGICAL FACTORS THAT MAY PREDISPOSE TOWARDS PARAPHILIAC BEHAVIOR

Some laboratory tests have helped us to learn more about organic factors associated with the presence of unusual sexual appetites and about biological "risk factors" which may predispose to difficulty in controlling sexual behavior. There is a great deal of animal and human research relevant to these and related issues.

Persons vary in sexual orientation and in the nature of their sexual desires. Although in the past, most psychiatric theories have postulated that differences in sexual interests are primarily the product of early life experiences, this hypothesis has not been proven. In animals, biologic factors play a major role in influencing sex-related activities. Most dog owners, for example, are well aware of the fact that female dogs become sexually responsive to male dogs only while in "heat" (estrus). At such times, in response to the odor of chemical substances that are secreted by the female, which can be measured in a laboratory, the males themselves become much more sexually assertive.

The degree and manner by which biologic factors, measurable in the laboratory, influence human sexuality is not entirely clear. This issue has been discussed by several researchers in *The Psychobiology of Sex Differences and Sex Roles* [6]. Goy and McEwen have suggested that biologic factors may contribute more to human sexual experience and behavior than previously appreciated [7]. In support of such a contention Money has published data which suggest that females exposed prenatally to high dosages of androgen may, as adults show patterns of psychosexual development more typically seen in males [8]. Recently Pillard summarized data suggesting there may be a genetic predisposition towards male homosexuality [9].

In 1982 researchers reported finding frequent lutenizing hormone abnormalities in a group of transsexuals [10]. Other research conducted in Czechoslovakia suggested that the development of sexually "deviant" behavior, such as sadomasochism, exhibitionism, or fetishism seemed sometimes to be correlated with brain injury or cerebral infection occurring during the first few years of life [11]. Unfortunately, in clinical situations involving the evaluation of men with unconventional sexual interests such as exhibitionism, pedophilia, raptophilia, transvestism, or voyeurism, genetic and other biologic factors have frequently gone unassessed.

With such information in mind, we performed a variety of laboratory tests on a group of paraphilic men [3]. Several areas of biologic functioning appeared particularly relevant. Genetic karyotyping was thought to be important since the genes which determine anatomical sexual gender are contained on the X and Y chromosomes. Endocrine assessment was considered necessary since certain hormones are suspected to be of relevance to sexual phenomenology including testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogens, and progesterone. We studied brain structure by means of computerized axial tomography (CT scan), and brain-wave activity by electroencephalogram (EEG) recordings.

Table 2. Recommended Laboratory Tests in Looking for Biologic Abnormalities in Paraphilic Patients

1. EEG
2. CT Scan
3. Testosterone
4. Estrogens
5. Progesterone
6. FSH
7. LH
8. Chromosomal karyotyping and analysis

A complete neurologic and physical examination should also be performed.

The series of laboratory tests shown in Table 2 (excluding estrogens and progesterone) was performed on a group of men meeting the DSM-III diagnostic criteria for paraphilia [2]. In 34 of 41 assessed cases, one or more significant biologic or clinical abnormalities were detected. These abnormalities (Table 3) included structural brain damage, hormonal irregularities, and chromosomal anomalies such as Klinefelter's syndrome. The finding of Klinefelter's syndrome in a number of homosexual pedophiles was particularly interesting since it is unclear whether Klinefelter's patients should be thought of as men with an extra X chromosome, or as women with an extra Y chromosome [2].

Although the biologic abnormalities found in this group of paraphilic patients occurred with greater frequency than would have been expected on a chance basis alone, similar tests were not performed on a group of men with conventional heterosexual interests. Future research should include such control groups looking for associations between biologic pathologies and the nature of an individual's sexual orientation and behavior. Researchers concerned with such issues may wish to employ the tests in Table 2 on their paraphilic patients to continue documenting the frequency of biological abnormalities in this population.

LABORATORY PROCEDURES

Measurement of Serum Testosterone

The measurement of androgen concentrations in blood (specifically testosterone concentrations) not only provides the clinician information about gonadal function, but also, along with serum FSH and LH values, can provide data on the competence of the whole hypothalamic-pituitary-testicular axis. Disturbances of this homeostatic regulatory system may be associated with the presence of unusual sexual interests or with difficulties in exercising adequate behavioral control over sexual appetite.

Plasma androgen concentrations have been measured in many ways. While such methods as enzymatic conversions to estrogen, double isotope derivative procedures, gas liquid chromatography, and competitive protein binding techniques have all been used, the development of the radioimmunoassay in 1969 has provided the best method to measure androgens in biological fluids [12]. Aulelta and others have explained how to suitably equip a laboratory in order to carry out radioimmunoassays of testosterone levels [13].

As shown in Figure 2, the measurement of testosterone levels in peripheral plasma by radioimmunoassay requires three basic elements: antibodies, radioactively labeled testosterone, and a plasma sample (usually first purified as described below) containing the unknown quantity of testosterone to be measured.

Initially the radioactively labeled hormone (the tracer) is added in excess to the antibody (AB) in a buffered solution. This tracer then binds to the antibody.

Table 3. Abnormal Laboratory and Clinical Findings in a Group of Patients with Various Sexual Disorders

Patient Diagnosis	Associated Findings
1. Erotic sadism	Occulomotor abnormality suggestive of basal ganglion dysfunction. Unexplained gait disturbance.
2. Homosexual pedophilia	Dyslexia, childhood lisp requiring speech therapy.
3. Homosexual pedophilia	Cortical atrophy, grand mal seizures, recurrent slow delta waves and sharp activity over frontal brain regions on EEG.
4. Hypersexuality	Elevated testosterone, family history of adrenogenital syndrome.
5. Homosexual pedophilia	Klinefelter's syndrome, Mosaic (90% 47XXY, 10% 46XY). Elevated FSH and LH. Low testosterone.
6. Homosexual pedophilia	Strabimus, childhood learning disorder.
7. Heterosexual pedophilia	Schizophrenia.
8. Exhibitionism	Elevated testosterone, prior history of coma X several months following head trauma, grand mal seizures.
9. Heterosexual pedophilia	Cortical atrophy (2° to trauma), right sided partial hemiparesis, visual spacial deficits.
10. Homosexual pedophilia	Elevated testosterone.
11. Heterosexual pedophilia	Near total blindness due to brain damage.
12. Heterosexual pedophilia	Elevated testosterone, mild ventriculomegaly and cortical atrophy most pronounced in areas of right sylvian fissure (by CAT scan), elevated 24 hour urine pregnanediol (3.1. Normal is less than 2.5 mg).
13. Homosexual pedophilia	Elevated LH. Generalized muscular hypotonia.
14. Paraphilic rape	Elevated testosterone, grand mal seizures.
15. Homosexual pedophilia	Elevated testosterone.
16. Hypersexuality	Cortical atrophy, cortical blindness, mild mental retardation.
17. Voyeurism	Elevated LH.
18. Homosexual pedophilia	Mosaic chromosomal pattern (97.5% XY, 2.5% XX), large heterochromatic region at centromere of autosome number 19 (polymorphic variant), low LH.
20. Homosexual pedophilia	46 XY, inversion 9 (p^+, q^-) Chromosome pattern. High LH.
21. Homosexual pedophilia	47 XXY chromosome pattern. Elevated testosterone, FSH.
22. Paraphilic rape	Elevated FSH.
23. Exhibitionism	Elevated LH.
24. Homosexual pedophilia	Low LH.
25. Heterosexual pedophilia	Elevated testosterone, FSH, and LH.
26. Homosexual pedophilia	Klinefelter's syndrome. Elevated FSH and LH. Low testosterone.
27. Heterosexual pedophilia	Elevated testosterone.
28. Homosexual pedophilia	Elevated testosterone.
29. Voyeurism	Elevated testosterone and LH.
30. Hypersexuality	Elevated testosterone, structural brain damage.
31. Homosexual pedophilia	Elevated testosterone, FSH and LH. EEG abnormality.
32. Transexualism and transvestism	Klinefelter's syndrome. Low testosterone.
33. Homosexual pedophilia	Elevated testosterone.
34. Homosexual pedophilia	Klinefelter's syndrome. Elevated FSH and LH. Low testosterone.

Normal (2 standard deviation) *testosterone* range in men = *275 to 875* ng/100 ml. Normal *FSH* in males = *9 to 369* ng/ml. Normal *LH* in males = *22 to 78* ng/ml. No associated abnormalities were detected in 7 other patients with sexual disorders who were also assessed.

When the unknown sample is added, it displaces some of the radioactively labeled tracer from the antibody in proportion to the amount of hormone in the sample.

The radioactively labeled tracer which is displaced is referred to as the "free hormone." After ample incubation time, this free hormone can be removed from the bound hormone and the amount of radioactivity that it emits can be measured by a scintillation counter. By comparing this count to those obtained from samples containing known quantities of hormone, one can calculate, using standard curves, the amount of hormone that was present in the sample of serum tested.

In order to perform a radioimmunoassay procedure, it is first necessary to obtain antibodies to testosterone. Because testosterone is of too low a molecular weight to act as an antigen by itself, it must first be linked to a larger protein molecule in order to evoke an antibody response. The necessary antibodies are usually

produced by injecting rabbits or sheep with testosterone linked with bovine serum albumin (BSA). This procedure yields a high titer of immunogens which have a high affinity for testosterone and dihydrotesterone but which will not cross-react with estrogens, progestens, or other steroids [12]. Testosterone antibodies are commercially available or they may be made by injecting rabbits or sheep with commercially available testosterone–BSA conjugates [13].

The second element needed to perform a radioimmunoassay procedure is radioactively labeled testosterone. At one time tritiated steroids were used for this purpose. However, these are now generally being replaced by radioiodinated steroid derivatives. I^{125} labeled steroids give a high level of sensitivity and their radioactive output is easily countable. They can also be used in the presence of high antiserum dilutions [14]. I^{125} labeled testosterone is readily available commercially; its

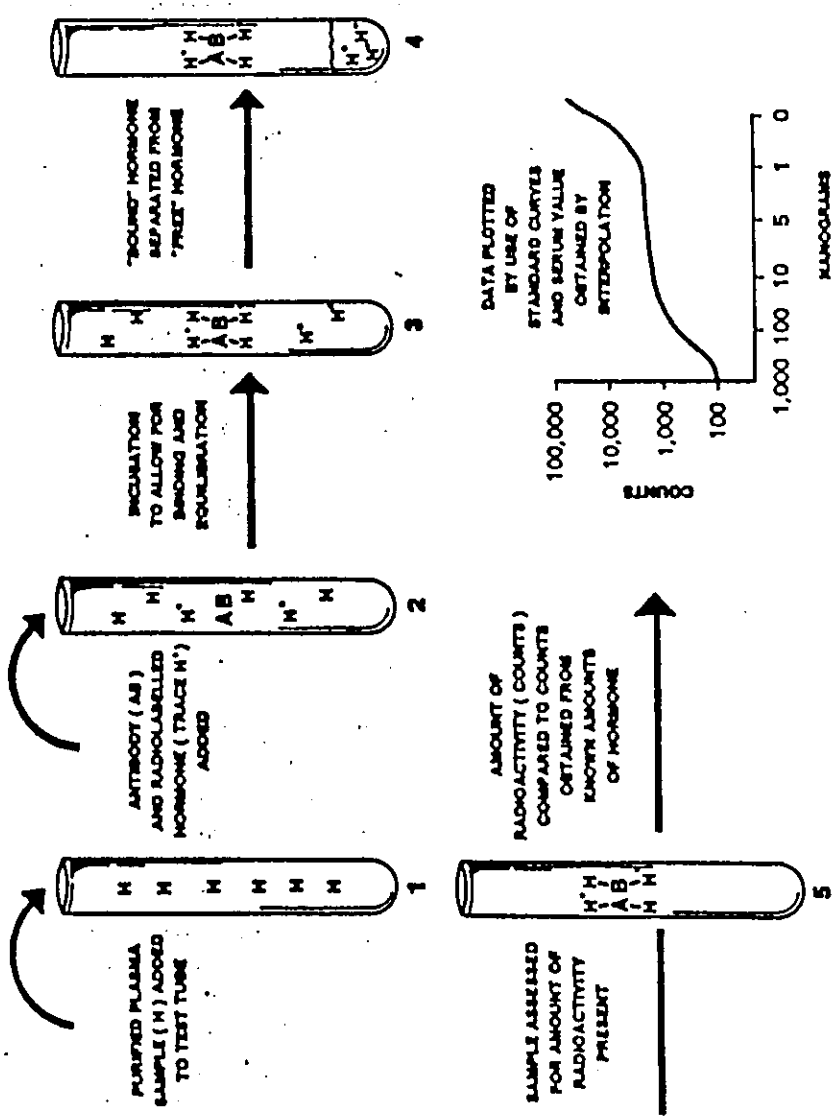

Figure 2. Measurement of testosterone levels by radioimmunoassay (following purification).

inclusion in radioimmunoassay kits has made measurements using this ligand routine.

The third element needed in doing radioimmunoassays is a sample of serum containing testosterone. Most radioimmunoassays are capable of measuring testosterone levels in as little as 0.5 ml of serum. However, ordinarily for ease of collection a 10 ml glass stoppered tube containing sodium heparin is used. In most hopsitals, heparinized tubes contain a green topped stopper. Ideally, blood should be obtained before 8 AM since marked diurnal variations in plasma testosterone levels have been reported and sampling at this time ensures determinations during peak levels [15]. Fasting samples are not necessary, and no commonly prescribed drugs (with the exception of sex steroids) seem to interfere with this assay.

In order to obtain accurate testosterone measurements, the sample of the patient's blood must have first been purified (before having been exposed to the mix of testosterone antibodies and radioactively labeled testosterone) to the plasma of proteins and other steroids such as dihydrotestosterone which would interfere with binding to the antibody. This is usually done by extracting one ml of the sample with an organic solvent and then purifying it by standard chromatographic methods [12]. Most antibodies are unable to distinguish testosterone from dihydrotesterone because they cross-react with both steroids.

Once plasma testosterone levels have been determined from a given patient's blood, the results can be compared to data obtained from a control population. It must be cautioned that in some centers the normal range of testosterone has been determined by sampling a population of presumably healthy men (usually between the ages of 20 and 60), sometimes numbering as few as 20. By convention, any value falling within the two standard deviation range of such a sample is then considered normal. As shown in Table 4, at our hospital, the two standard deviation range of testosterone in men is between 275 and 875 ng/100 ml of blood. The mean is 575 ng/100 ml with a standard deviation of ± 150. Any value above 875 is considered elevated. It is usually good practice to repeat any abnormal value at least once to ensure the accuracy of the finding.

There are a number of medical conditions associated with low levels of testosterone. Adrenal, gonadal, or pituitary tumors are the known major medical causes for excessively elevated androgen levels.

Measurement of FSH and LH

Serum FSH and LH levels can also be obtained by using radioimmunoassay methods. In this case, antibodies generated against gonadotropins must be employed. Radiolodinated hormones can again be used as tracers.

In obtaining blood to determine FSH or LH levels, a 10 ml nonheparinized (red capped) tube is generally used. A nonheparinized tube is used because this assay makes use of the serum rather than the plasma fraction of blood. The sample of blood may be obtained at any time, but early morning is preferable. Once again

Table 4. Normal (Two Standard Deviation) Ranges of Blood Levels in Men and Women of Testosterone, FSH, and LH

	Men	Women
Testosterone	275–875 ng/100 ml	23–75 ng/100 ml
FSH	9–367 ng/ml	97–425 ng/ml (except midcycle)
LH	22–78 ng/ml	15–99 ng/ml (except midcycle)

normal values are considered to be those falling within the two standard deviation range as established by using a group of apparently healthy adults as the reference population. Our normal two standard deviation range for males for serum FSH is between 9 and 367 ng/ml and for serum LH is between 22 and 78 ng/ml. Moudgel and others give a complete description of radioimmunoassay methods for measuring the amount of FSH and LH (as well as the amount of estrogens and progesterone) present in blood [16].

Karyotyping

It is now reasonably well established that patients with particular kinds of chromosomal anomalies are more at risk for unconventional sexual appetites, feelings of gender dysphoria, or commission of a sex offense than persons whose chromosomal pattern is nonpathological [17]. Karyotyping, a procedure first used in the late 1950s, consists of the visual examination of chromosomes and the determination of their number and structure [18]. Most individuals have 23 homologous pairs, or 46 chromosomes, in each somatic cell of their body. Each chromosome contains about 100,000 genes. Twenty-two pairs are similar in appearance in males and females and are termed autosomes, while the 23rd pair, the so-called "sex chromosomes," determine anatomic gender. If a fertilized oocyte is to become a male, ordinarily the 23rd chromosome pair will by an XY; if it is to be a female, that pair will by an XX.

In order to perform karyotyping, 3 to 5 ml of blood is collected in a heparinized test tube. The blood is used in order to obtain leukocytes. This sample should be kept at room temperature and may sit overnight before being processed.

Briefly summarized, the karyotyping procedure consists of placing leukocytes in a 3 day tissue culture with phytohemmagglutin, an extract of the red bean. This substance stimulates the white cells to divide in culture by 72 hours. Once mitosis has begun, a dilute solution of colchicine is added which stops mitosis at metaphase. This allows the visualization of chromosomes under a microscope after the

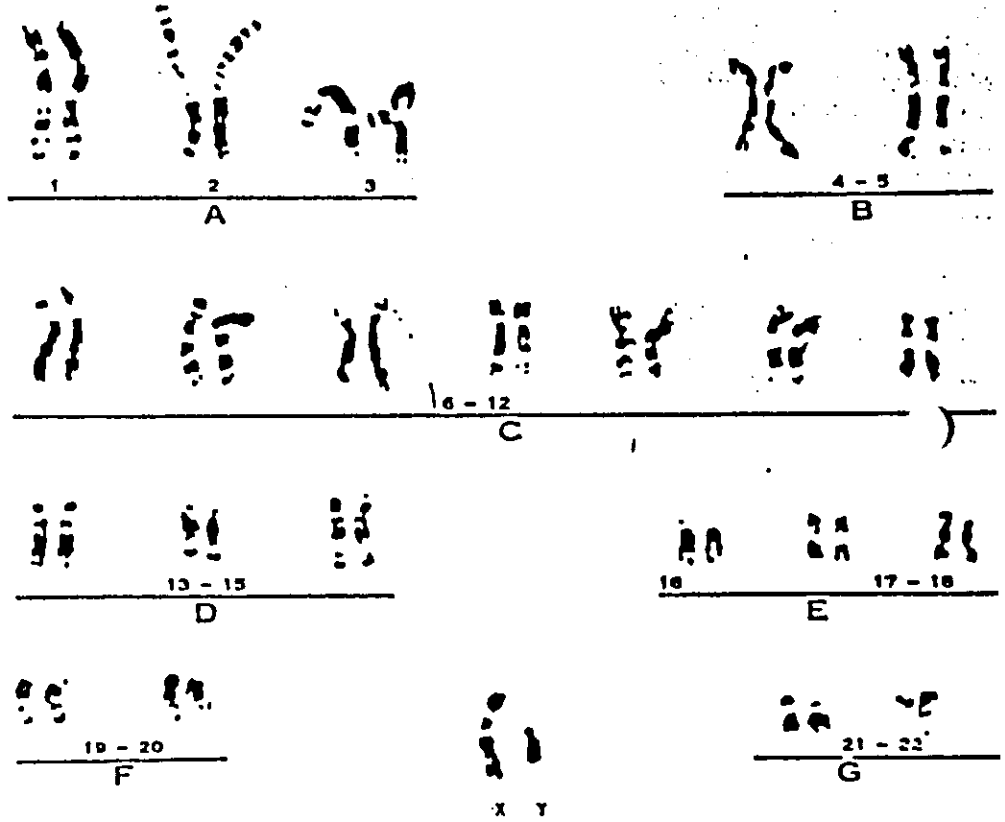

Figure 3. A normal male (46 XY) karyotype.

cells have been fixed and stained. Photographs of the chromosomes are then taken. The chromosomes are cut from the photographic print, matched into homologous pairs, mounted on cardboard and analyzed for number as well as structure. A normal male karyotype is shown in Figure 3.

Techniques such as banding and autoradiography have been developed to identify specific abnormalities *within* a given chromosome. These additional procedures increase the expense of chromosomal analysis. Complete instructions for culturing human leukocytes, composing karyotypes, and interpreting the results can be found elsewhere [18,19].

Chromosomal karyotyping and analysis reports whether the number of chromosomes present are normal in quantity and whether within each chromosome there are abnormalities of the constituent gene segments.

THE PET SCANNER AS AN INVESTIGATORY PROCEDURE: WHAT HAPPENS IN THE BRAIN DURING EROTIC AROUSAL?

There is reason to believe that the brain differs from one region to another in ietabolic activity during sexual arousal. As discussed below, and elsewhere in this :xt, the recent development of the PET scanner provides a new technology that iay be capable of documenting such differences [20,21]. Thus, the PET scanner iay be able to provide knowledge about (1) how this "organ of thought and :eling," the brain, functions at such times, and (2) whether the brains of persons 'ho experience unconventional sexual appetites, or who have difficulty controlling ieir sexual behaviors, function differently than the brains of persons who seem :ss troubled in these ways.

It is already known that certain brain structures (eg., the area preoptica in the ypothalamus) accumulate relatively large amounts of sex related hormones such s testosterone, whereas other areas (such as the limbic system) do not [22]. It is lso known that stimulation or ablation of *specific* brain areas can lead to dramatic hanges in the amounts of such hormones released into the blood stream [23]. In ddition, stimulation, or ablation, of specific brain regions in animals is correlated vith obvious changes in the frequency of various kinds of sexual behavior [24].)amage to certain areas of the brain in humans has also been associated with the levelopment of aberrant sexual activity [25]. It seems likely then that certain areas)f the brain may be more involved than others during erotic arousal.

Lesions made in the area preoptica of the hypothalamus, an area particularly rich in sex hormone receptors, have been shown to lead to a decrease in the frequency of sexual behavior in animals, without affecting either perceptual-motor capabilities or circulating testosterone levels [26]. Estrogen applied locally to specific hypothalamic sites in male rats (but not other sites) leads to a lordotic response, i.e., a backward elevation of the pelvis that facilitates female intercourse [27]. Testosterone implants in certain hypothalamic sites can reactivate mating behavior in castrated male animals, but similar implants in other brain sites cannot [28]. Electrical stimulation of the dorsal part of the lateral area preoptica causes almost uninterrupted mounting and frequent ejaculations in male rats [29].

As long ago as 1939 Kluver and Bucy described a syndrome in cats produced by bilateral lesions to the temporal lobes that resulted in intensified indiscriminate sexual behavior [30]. Schreiner and Kling have shown that this "hypersexual" activity can be abolished by castration but reinstituted with testosterone replacement therapy, suggesting that the behavior is sex hormone related [31]. They have also demonstrated that lesions applied to specific sites in the ventromedial nucleus of the hypothalamus can likewise abolish this "hypersexual" activity.

In 1966 a team of neurosurgeons performed sterotactic brain surgery on a homosexual pedophile, making a lesion in the ventromedial nucleus of the hypothalamus in the same area that Schreiner and Kling had ablated in cats [32]. The patient subsequently indicated that his erotic fantasy life was virtually abolished, and that he had lost his pedophilic urges. Orthner reported that substantial sex drive reduction had been achieved in 34 sex offenders treated neurosurgically by making lesions in analogous brain regions [33]. Although these claims of therapeutic success have been questioned by some, Freund feels that these surgical teams may have obtained genuine success [34]. A recent governmental task force appointed to consider the topic of psychosurgery in the United States concluded that it may have therapeutic promise [35]. If PET scanning, or similar techniques, can confirm that certain areas of the brain do indeed selectively increase in metabolic activity in association with erotic arousal, and, if it suggests that these areas differ depending upon the nature of one's sexual interests, a more rational basis for providing therapy to those persons who experience unconventional erotic urges potentially harmful to themselves or others may eventually become possible.

ANALYSIS OF PET SCANNING RESULTS

PET scanning requires that a patient be administered a small amount of radioactively labeled material such as C-11 deoxyglucose. A computer attached to Geiger counter type sensors placed around the patient's head then produces a series of cross sectional pictures of the brain which vary in color according to the amount of glucose being utilized at any given anatomic site (Figure 4). PET scanning can be performed twice on any given patient; first prior to and then during erotic arousal with a penile transducer being used to confirm arousal.

Table 5 summarizes categories of data that can be generated by performing PET scanning before and during erotic arousal on men with conventional and unconventional sexual interests. That table also includes categories that could be generated by repeating PET scanning after initiation of antiandrogenic medication treatment.

PET scan results of the sort which would fit into such a table can be reported (either based upon the visual observations of an experienced radiologis.) by means of direct analysis of the computer-stored data) in terms of the relative density of radioactive output per defined area of the brain. When these assessments are based upon visual observations, they reflect an assessment of the type and intensity of a particular color as seen on the computer-produced picture of a given brain region. However, such subjective assessments are unnecessary because observations from a given brain region (or Pixel) can be quantified by actually totaling the counts of radioactivity from that region and then comparing them to counts from other regions or to counts from the brain as a whole. Various regions of the brain can be systematically compared in this way. Thus, each of the cells in Table 5 can be compared with one another for any given brain region, with differences in mean group densities between men with conventional vs unconventional sexual interests

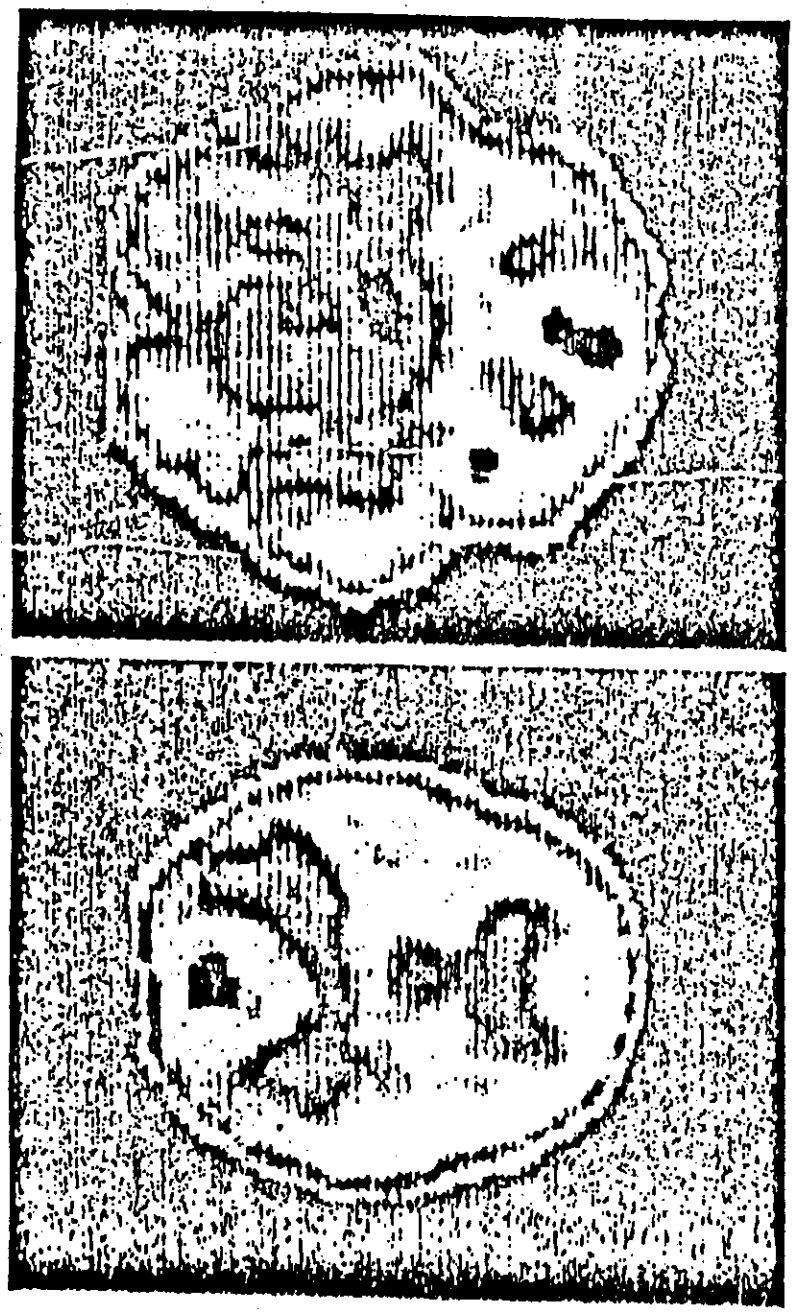

Figure 4. A cross-sectional picture of the brain at two levels produced by PET scanning.

Table 5. Summary of Categories of Data That Can Be Generated by Performing PET Scanning

			Participant number	Before antiandrogenic medication is given	After antiandrogenic medication is given
Persons with unconventional sexual interests	EPVTO	Prior to sexual arousal	A_1		
			A_n		
	EPVTO	During sexual arousal	A_1		
			A_n		
Persons with conventional sexual interests		Prior to sexual arousal	B_1		
			B_n		
		During sexual arousal	B_1		
			B_n		

E, exhibitionist; P, pedophiles; t, transvestites; v, voyeurs, O, other paraphilias

being assessed for statistical significance. When comparisons are made between data obtained prior to and during sexual arousal, each study participant can be used as his own control. If a sufficient number of men in each category of paraphilia (exhibitionism, pedophilia, voyeurism, etc.) can be obtained, statistical comparisons can be made among these groups as well.

In studies where participants are asked only to *imagine* erotically stimulating imagery in order to attain a state of sexual arousal, a different pattern of regional brain activity may occur then would be the case in the presence of olfactory, visual, tactile, or other forms of erotic sensory stimulation. Regional brain metabolism during sexual climax (as opposed to during the arousal or desire phases) may also be different. Although at present only radioactively labeled glucose is ordinarily used in performing Pett scanning, in the future labeling of testosterone, FSH, or LH may also be possible.

PET scanning may help provide answers to the following questions. Are there differences between groups of patients (eg., heterosexual exhibitionists vs homosexual pedophiles) in regional brain metabolism when *not* sexually aroused? What areas of the brain become metabolically active during sexual arousal? Do these areas differ among persons who experience different sexual interests? What are the effects upon brain metabolism during sexual arousal of various sorts of sensory inputs such as visual, auditory, or olfactory stimulation? Does metabolic brain activity change during sexual climax? What are the effects of antiandrogenic medication treatment upon regional brain metabolism during sexual arousal?

RATIONALE FOR USING TESTOSTERONE-LOWERING METHODS TO TREAT PARAPHILIAS: EVIDENCE OF EFFICACY

Sex offenders make up a significant proportion of many prison populations at major expense to the public. Thus, the question of whether or not persons who experience unconventional erotic desires, such as pedophiles, exhibitionists, and some rapists can be helped by antiandrogenic medication treatment is important.

It is known from simplest phenomenology that people do not decide voluntarily what will arouse them sexually. Recently Abel reported that prior to therapy a number of rapists seemed unable to prevent themselves from obtaining an erection while listening to descriptions of coercive sexual acts, whereas most nonrapists could [36]. Quincey showed that some rapists can be distinguished from nonrapists by the ratio (as measured by penile plethysmography) of their erotic arousal while listening to descriptions of coercive versus noncoercive sexual acts [5]. Abel's and Quincey's data suggest two possibilities. (1) Some men may rape as a consequence of difficulty suppressing their sexual urges. (2) Some rapists may become relatively more aroused than other men by coercive (as opposed to noncoercive) sexual acts. If this is so, treatments which lower sexual appetite may be helpful.

One of the early methods used in an attempt to decrease sexual appetite was bilateral orchiectomy which lowers the hormone testosterone. In animals, although individual differences in the rate of change in sexual behavior following orchiectomy are frequent, castration invariably results in an eventual decrease in most forms of sexual activity [34].

Several studies have looked at the recidivism rate of sex offenses following castration in humans. Unfortunately, few such studies stipulated whether the sex offenders treated in this manner had previously been experiencing unconventional erotic urges. Nevertheless, these studies are relevant to the question of whether or not treatment with antiandrogenic medication is likely to be helpful.

Sturup and others conducted over 4,000 follow-up examinations on 900 castrated sex offenders in Denmark over a 30-year-period and reported that only

1.1% definitely recidivated [37]. If unclear cases were included, the recidivism rate was 2.2%. Wiffels reported comparable findings [38]. Ficher Van Rossum reported similarly low rates on 307 Swedish patients [39]. Bremer found a 7.3% recidivism rate after 5 years among a group of 41 castrated sex offenders who, prior to treatment, had had a recidivism rate of 58% [40]. Additional data regarding the effects of castration upon recidivism are presented in an excellent review article by Freund [34]. Although there has been some debate about how to interpret these data, Freund concluded that this form of treatment, which is intended as a means of therapeutic sex drive reduction to facilitate self control, and not as punishment, has been successful.

Besides documenting changes in recidivism rate, a number of investigators have obtained self-reports from castrated sex offenders regarding potency. In many cases, following castration some degree of erotic desire and the capacity to perform sexually remained [39]. Freund pointed out that this does not necessarily present a problem in terms of treatment, however, since the surgery fulfills its intent if it decreases the sex drive sufficiently to enable the patient to refrain from acting upon unacceptable erotic urges [34].

Two medications which have been used as sexual appetite suppressants are medroxyprogesterone acetate (MPA) and cyproterone acetate (CPA). Like castration, both lower testosterone levels. However, unlike castration neither results in a compensatory elevation of FSH or LH by the pituitary gland, suggesting that they may have a direct effect upon brain activity.

Langerin and colleagues have reported two double-blind studies using MPA [41]. In both cases MPA seemed to lower sexual libido. However, the dosages employed, route of administration, duration of treatment, and outcome measures utilized were not comparable to most clinical antiandrogenic treatment protocols. A double-blind investigation using CPA reported successful reductions in "deviant" sexual interests and libido, but a pharmacologically active placebo medication was not used for comparison purposes [42].

Table 6 shows changes in sexually "deviant" behavior in a group of 20 chronic paraphilic patients treated in a non-blind study with medroxyprogesterone acetate [43,44]. Fifteen percent of patients (3 of the 20) showed recurrences of deviant activity while taking the medication, indicating that it is not 100% effective. On the other hand, 85% of these men were apparently totally without further legal involvements while receiving medication, sometimes for periods as long as several years. Some patients in this study were self-referred, but most were referred by a physician or attorney subsequent to legal apprehension.

Most of the patients reported upon in Table 6 were not hospitalized to initiate treatment and were not required as a condition of probation to take medication. In time, many became noncompliant, sometimes because they believed themselves cured. Currently, most of our patients are hospitalized for 3 or 4 weeks at the beginning of therapy and subsequent outpatient compliance has improved dramatically.

Table 6. Changes in Paraphilic Behavior During and After Treatment With Antiandrogenic Medication[a]

Patient	Age (years)	Diagnosis	Average frequency of sexually deviant behaviors before treatment[b]	Drug treatment		Occurrence of sexually deviant behaviors	
				Length	Maximum dosage	During treatment	After treatment
1	34	Homosexual pedophilia	Once/week	5 years, 9 months	500 mg/week	None	Treatment dropout; no relapse less than 1 year after treatment
2	31	Homosexual pedophilia	Twice/month; 1 known arrest	1 year	300 mg/week	None	Treatment dropout; relapsed less than 1 year after treatment
3	30	Heterosexual exhibitionism	Twice/week	10 months	250–300 mg/week	None	Treatment dropout; relapsed more than 1 year after treatment
4	34	Homosexual masochism	4 times/week	3 months	200 mg/week	None	Treatment dropout; relapsed less than 1 year after treatment
5	27	Bisexual pedophilia	Twice/week	3 months	400 mg/week	None	Treatment dropout; relapsed more than one year after treatment
6	43	Transvestism; homosexual incest	7 times/week; 2 incidents	1 year, 4 months, intermittently	150 mg every other week	None	Relapsed less than 1 year after treatment
7	52	Heterosexual sadism	Once every 2 weeks for 25 years	3 years, 5 months	600 mg/week	None	Treatment continues; no relapses
8	29	Homosexual pedophilia	Twice/week; 6 arrests in 6 years	10 months	500 mg/week	None	Treatment dropout; relapsed less than 1 year after treatment
9	36	Homosexual pedophilia	Once every 2 months; 4 arrests in 6 years	2 years	500 mg/week	None	Treatment continues; no relapses
10	56	Homosexual pedophilia	Once/week; 14 arrests in 29 years	3 years, 9 months	300 mg/week	Relapsed	Treatment continues
11	40	Homosexual pedophilia	Twice/week; 7 known arrests	4 years, 2 months	400 mg/week	None	Treatment continues; no relapses
12	45	Voyeurism; heterosexual pedophilia	— Twice/week; 5-8 arrests; numerous institutionalizations	5 years, 3 months	300 mg/week	None	Relapsed less than 1 year after treatment; treatment now resumed
13	27	Homosexual pedophilia	Twice/week since age 10	5 years, 9 months	200 mg/week	None	Treatment completed; no relapse more than 1 year after treatment
14	41	Homosexual pedophilia	Once/month; numerous arrests; 4 convictions; 4 reported parole violations	3 years, 8 months	500 mg/week	Relapsed	Treatment continues
15	37	Homosexual pedophilia; exhibitionism	Record unclear; probably several incidents/year	3 years, 9 months	350 mg/week	None	Treatment completed; no relapse less than 1 year after treatment
16	26	Homosexual pedophilia	Once/week	1 year, 1 month	200 mg/week	None	Treatment dropout; relapsed more than 1 year after treatment
17	24	Heterosexual voyeurism	Once/month	1 year	400 mg/week	Relapsed after alcohol consumption	Treatment continues; in prison
18	40	Heterosexual exhibitionism	Five times/day since age 11; first arrest at age 21; numerous others	2 years, 2 months	200 mg/week	None	Treatment dropout; relapsed less than 1 year after treatment
19	29	Heterosexual exhibitionism	Twice/week	2 years, 1 month	250 mg/week	None	Treatment dropout; relapsed less than 1 year after treatment
20	46	Heterosexual exhibitionism	Four times/week; binges of 20/day	2 years, 3 months	300 mg/week	None	Treatment continues; no relapses

[a]Sexually deviant behavior was considered to have occurred if the patient was accused of having or admitted having a deviant sexual contact (for example, an episode of public genital exposure). Any occurrence of such behavior was scored as a relapse once treatment had been initiated, even if it did not come to the attention of the law as an official complaint.

[b]Based on institutional records and patients' statements.

[c]Study participants who stopped taking medroxyprogesterone acetate did so against medical advice, except in the cases of patients 13 and 15. Some patients were irregularly compliant with medication even during the period when it was being prescribed.

The data presented in Table 6 show clearly that in most cases when paraphilic patients discontinue medications they relapse. This supports the hypothesis that this form of treatment is neither a cure nor a temporary catalyst to be used until psychotherapy can become effective. Rather, for the majority of patients, the medication appears to act as a sexual appetite suppressant. If deviant hungers are allowed to return, most patients seem again to be at risk. In a few cases, patients have reported that MPA fails to significantly decrease their sexual drive. Why this should be so is not known. Currently we are treating approximately 70 paraphilic patients on an outpatient basis with a combination of group therapy and antiandrogens. Less than 10% have recidivated, and none have committed a physically violent crime.

ANDROGENS AND FACTORS RELATED TO THEIR MEASUREMENT

Thus far the discussion has concerned (1) what laboratory tests can be used to look for biologic pathologies in paraphilic patients, (2) PET scanning as a potential procedure for documenting what goes on in the brain during erotic arousal, and 3) the rationale for and efficacy of using testosterone-lowering methods to treat some "sex offenders." In closing, a discussion of androgens and antiandrogens and of the laboratory protocol used to assess for possible side effects of testosterone-lowering treatments will be presented.

Classically, an androgen is defined as a substance which stimulates the growth of the male reproductive tract [45]. These substances, all of which are steroids, are secreted 90% by the testes and 10% by the adrenal cortex [46]. Testosterone is the major androgen produced by the testes of man, and it is also the androgen present in highest concentration in the peripheral bloodstream [47]. Testosterone is the hormone which causes the fetus to take on a male appearance. It is also the androgen which increases in males at puberty resulting in increased growth of facial and pubic hair, deepening of the voice, thickening of bodily muscles, and increased sexual interests.

The biochemical pathways of androgen biosynthesis by the testes are now well established as shown in Figure 5. Essentially, steroid metabolism in the testes consists of distinct steps requiring specific enzymes and their cofactors [48]. Whether a hormonal endproduct such as testosterone is produced depends upon the presence or absence of the necessary enzymatic components within the tissues of a particular organ.

Cholesterol is the key precursor of all steroid hormones synthesized by the testes. This cholesterol can originate from the circulation, or be synthesized from acetate by Leydig cells in the testes themselves.

Once produced and secreted, testosterone can undergo two additional biochemical conversions. (1) It can be reduced to 5 alpha-dihydrotesterone (DHT) by

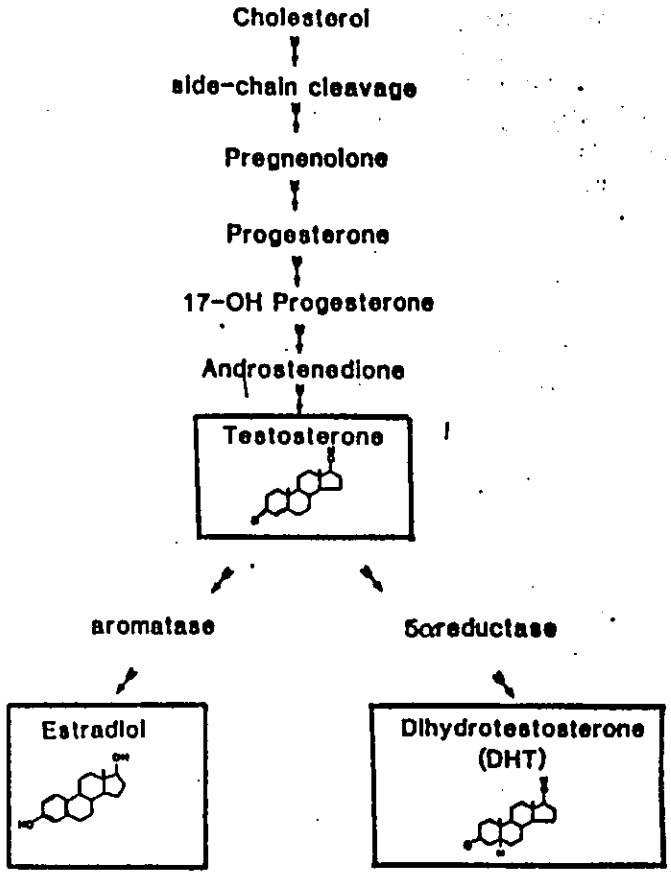

Figure 5. Biochemical pathways of androgen biosynthesis by the testes.

a intracellular enzyme known as 5-alpha-reductase. DHT, which is an even more potent androgen than testosterone, is the biologically active intracellular androgen in some tissues. It is present in the brain cells of many species and it may play a role in the functioning of the central nervous system [49]. (2) Alternatively, testosterone (as well as androstenedione) can be converted to estrone and estradiol respectively (rather than to DHT). The series of reactions by which testosterone is converted to estradiol is collectively referred to as aromatization. Many tissues including brain, skin, fat, and liver are capable of converting androgens to estrogens, and it has been shown that the majority of blood estradiol and estrone comes from the aromatization of circulating androstenedione and testosterone [50]. Up to 60 mg/day of estrone and 40 mg/day of estradiol are produced in normal healthy men [51].

Once synthesized, testosterone enters the systemic circulation bound mainly to serum proteins. These proteins include testosterone estradiol binding globulin (TeBG), which binds 30% of serum testosterone, albumin (which binds 67%), and other plasma proteins, which transport the remainder of bound hormone. Only about 2% of circulating testosterone is free in the plasma [52].

Classically, it has been taught that in order for a hormone to be physiologically active, it must be present in the blood stream in pure form, free from serum binding globulins or other proteins that ordinarily transport substances through the circulation. Recently, however, this formulation has been questioned, and it is now uncertain whether it is the free or bound component of a hormone circulating through the plasma which is actually responsible for its biologic effects in some instances. Thus, as described earlier, in the Hopkins laboratory total plasma testosterone (ie., bound plus free) is ordinarily ascertained. This value is a good indicator of an individual's androgenic status, and it is easily measured. Tests currently available to assess free hormone are time consuming, cumbersome, and frequently inaccurate.

Like other steroid hormones, androgens are metabolized by the liver and the breakdown products are eventually secreted by the kidneys (in the form of glucuronides or sulfates) into the urine [12]. A small amount of testosterone (about 6%) enters the enteroheaptic circulation and is excreted into the feces [51].

Total plasma testosterone values obtained from patients with severe liver disease may be somewhat depressed. This is so because the carrier proteins to which most of the testosterone present in the circulatin binds are produced by the liver, and they may be produced in lesser amounts in severe liver disease. Thus, the protein-bound component of total plasma testosterone will be lower. In addition, a malfunctioning liver may have a reduced ability to clear normally present amounts of testosterone from the plasma. This can result in a transient elevation of testosterone which in turn will suppress FSH and LH production by the pituitary, thereby in the long run lowering testosterone production by the testes.

The measurement of urinary ketosteroids reflects mainly adrenal function. Therefore, urinary 17-ketosteroid determinations are not clinically useful indicators of testicular function [51].

ANTIANDROGENS AND THE LABORATORY PROTOCOL

The first compound used clinically to antagonize the biologic actions of male sex hormones was diethylstilbesterol. It was initially used in 1943 for its antiandrogenic effects in the treatment of prostatic cancer [53]. It and similar compounds have found clinical us in such conditions as hirsutism, precocious puberty, virilization, acne, male pattern baldness, and breast carcinoma. Some antiandrogens have been proposed as possible male contraceptives [54]. Compounds used as antiandrogens include estrogens and progestins, as well as several nonsteroidal substances.

The ideal antiandrogen for clinical use would be a substance that possesses low toxicity, high potential as a "sexual appetite suppressant," and negligible feminizing effects. One compound which may come close to meeting these three criteria is medroxyprogesterone acetate (Depo-provera). Its chemical structure is shown in Figure 6.

Medroxyprogesterone acetate (MPA) is a potent synthetic progestin. When used as a sexual appetite suppressant, this hormone can be injected intramuscularily in doses as high as 800 mg/week. The ususal starting dosage is 500 mg/week. Following injection, this depot medication binds to muscle and is slowly released into the bloodstream, where it maintains fairly constant serum levels. The dosage can be titrated to avoid impotence and the medication is not feminizing. The 400 mg/ml concentration has greater bioavailability and is less painful when injected than is the 400 mg/ml solution. No more than 250 mg/ml should be administered into a single injection site.

The major side effects of MPA are weight gain and mild lethargy, but cold sweats, nightmares, myalgia, dyspnea, hyperglycemia, azospermia, hypertension, and breast cancer in female beagle dogs have all been reported. Hypertension sometimes becomes sufficiently problematic as to require concommitant treatment. Currently it is believed that the side effects produced in humans are fully reversible after the drug is discontinued, but MPA has not been in clinical use long enough to be certain that this will remain true.

The mechanism by which MPA lowers serum testosterone has been the subject of a number of recent studies. It appears that MPA works in several ways. It is known, for example, that MPA inhibits gonadotropin release from the pituitary

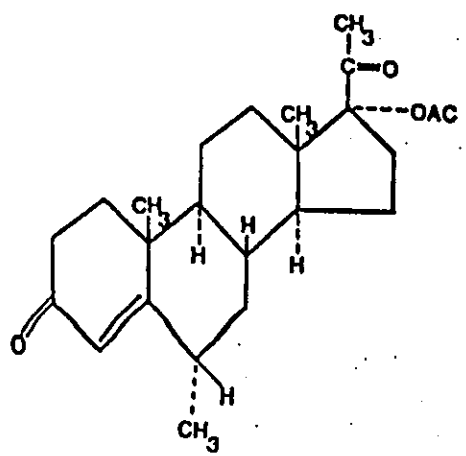

Figure 6. Chemical structure of medroxyprogesterone acetate (Depo-provera).

and [55,56]. MPA also increases the metabolic clearance rate of testosterone nd increases hepatic testosterone reductase activity, thereby facilitating removal f testosterone from the plasma by the liver [57,58]. Besides lowering testoster- ne, MPA decreases spermatogenesis [59,60].

MPA may bind to peripheral androgen receptors on various target organs and may also interfere with the conversion of testosterone to the more potent andro- n, DHT. Some of the possible sites, and mechanisms of action, of MPA are de- cted schematically in Figure 7.

Apparent changes in sexual appetite resulting from injections of MPA may be lated more to its central effects upon the brain than to its effect upon circulat- g serum testosterone levels. This is supported by the observation that some pa- ents report a subjective decrease in sexual appetite when the dosages of MPA ven are beyond those which would lower serum testosterone any further. When PA is used to increase sexual self-control, dosage levels should be adjusted accord- g to the patient's subjective reports of changes in the intensity and frequency unacceptable erotic preoccupations rather than by monitoring serum testoster- ne levels.

Ordinarily, prior to initiating antiandrogenic medication treatment baseline vels of FSH, LH, and testosterone should be assessed and follow-up tests should conducted every six months to document current levels. Every six months an MA-12 should also be performed to be certain blood sugar, kidney function, and ver functions are stable and not adversely effected by the treatment regime. lood pressure and body weight should be monitored weekly. This protocol, along ith recommended dosage and injection instructions, is summarized in Table 7. our clinic as part of their treatment protocol men receiving MPA to facilitate lf-control of sexual behavior are also expected to attend weekly group therapy ssions intended to try to reinforce their efforts to succeed. Group therapy ses- ons and medication injections are seen as a form of maintenance treatment rather an being seen as curative.

FUTURE CONSIDERATIONS

Because of the complex interaction of the hypothalamus, pituitary gland, and ne testes, many possibilities exist for pharmacologic interruption of testosterone roduction or for preventing its utilization. As shown in Figure 8, testosterone pro- uction by the Leydig cells of the testes is controlled by LHRH which is produced y the hypothalamus and stimulates the release of LH by the pituitary gland. Sperm production by the testes may also be controlled by FSH production from he pituitary gland and by another hormone produced by the testes itself called "inhibin," which inhibits FSH production).

Male sexuality seems related to the interaction (both constitutional and ac-

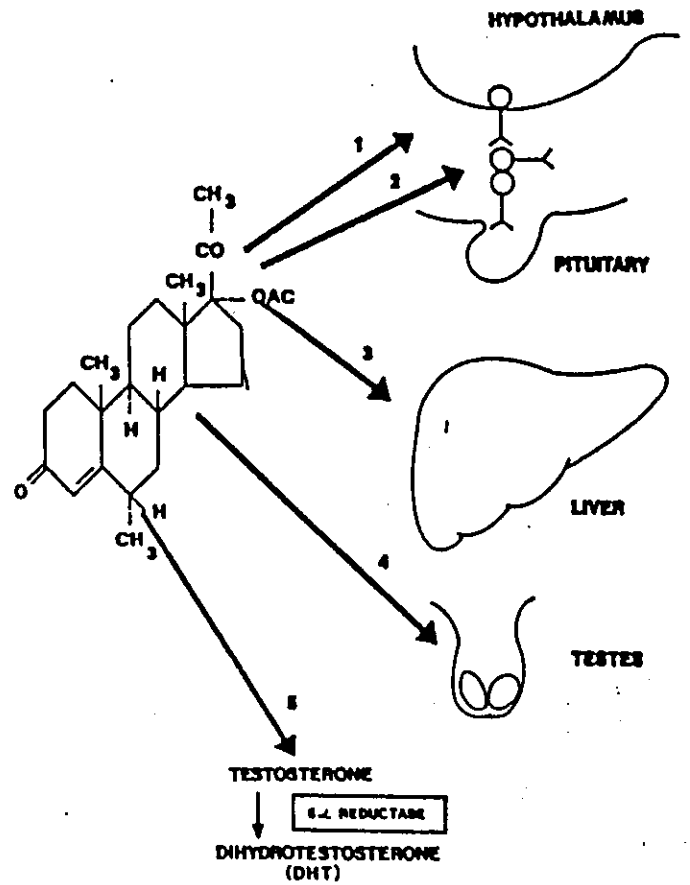

Figure 7. Possible sites of action of medroxyprogesterone acetate. (1) hypothalamic and higher cortical center inhibition; (2) inhibition of FSH and LH release from the pituitary gland; (3) increased hepatic testosterone reductase activity and increased metabolic clearance rate of testosterone by the liver; (4) decreased spermatogenesis and decreased testosterone production; (5) inhibition of the conversion of testosterone to DHT in various tissues and organs, including the central nervous system.

quired) between the central nervous system and the endocrine system. This interaction apparently develops rapidly in early prenatal life in monkeys, guinea pigs, and humans, and during the immediate postnatal period in rats [61]. At those times testosterone secretion from the testes causes actual structural brain changes believed responsible for the development of gender specific sexual behaviors in

Table 7. Recommended Protocol When Employing Antiandrogenic Medication to Treat Paraphilic Patients

Assessement prior to initiating ıtiandrogenic treatment	Assessments during antiandrogenic treatment	
Testosterone	1. Testosterone	once every 6 months
FSH	2. FSH	
LH	3. LH	
SMA_{12}	4. SMA_{12}	
CBC	5. CBC	
Physical examination	6. Physical examination	
Blood pressure	7. Blood pressure	once/week
Body weight	8. Body weight	
	Major side effects: weight gain, hypertension,	
	Minor side effects: hot flashes, cold sweats, lethargy, myalgias.	

Recommended starting dosage of medroxyprogesterone acetate:
(A) 500 mg IM once/week
(B) 100 mg/cc concentration (rather than 400 mg/cc)
(C) no more than 250 mg into a single injection site
(D) After 4 weeks titrate dosage according to patient's subjective reports.
(1) increase (up to 800 mg/week) if sexual urges are still too intense
(2) decrease if problems with side effects or sexual potency
Most of our patients are presently maintained at the 500 mg/week level.

animals and for the suppression in males of the monthly surge of FSH that is ordinarily seen in females [49]. Thus, some biologic changes possibly relevant to the regulation of sexual behavior may occur prenatally, making subsequent alterations difficult. Nevertheless, better methods of lowering troublesome sexual urges may be possible. For example, studies have shown that LHRH agonists can suppress testosterone production when given chronically [62]. The mechanism seems to involve supersaturation of receptors to the point where they no longer function. Since LHRH acts at the pituitary level, entry via the nasal route is possible. The use of LHRH nasal sprays in human females to treat infertility has been reported, but use in males to decrease testosterone production awaits clinical trials [63,64]. LHRH antagonists have also been synthesized, and they too hold promise for use in inhibiting testosterone formation [65].

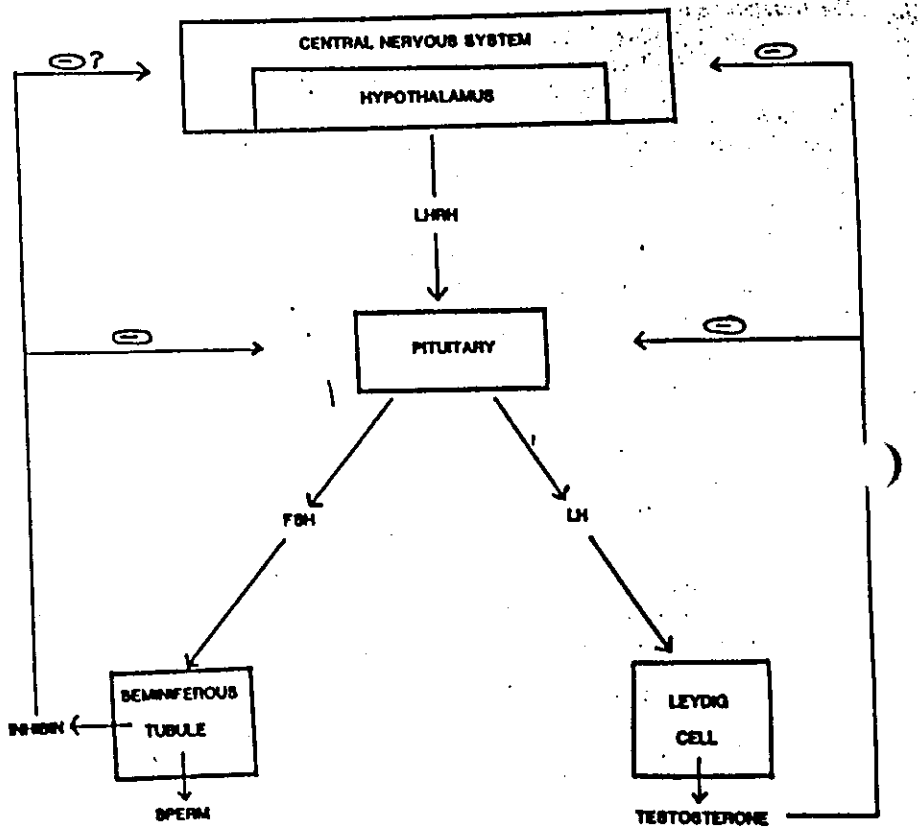

Figure 8. Homeostatic relationship between the hypothalamus, pituitary gland, and testes.

There is evidence that sometimes testosterone exerts biologic effects on the brain only after being converted in the central nervous system to estrogen via aromatization [49]. Aromatizable androgens, for example, can increase the frequency of mounting and lordosis in rabbits; nonaromatizable androgens cannot. ATD, an inhibitor of the anomatase enzyme (which converts testosterone to estrogen) blocks testosterone-stimulated copulatory behavior in rats. Thus, theoretically, in the future it may be possible to block the aromatization of testosterone to estrogen centrally, thereby inhibiting testosterone's action in the brain itself. This might have the benefit of avoiding side effects (such as azospermia) resulting from lowering testosterone production peripherally. The clinical application of this method awaits additional animal trials which will reveal whether aromatose inhibitors can enter the brain and inhibit the conversion of testosterone to estrogens in those areas thought to be related to sexual phenomenology and behavior.

CONCLUDING COMMENTS

Human experience and behavior, including sexual experience and behavior, results from the complex interaction of constitutional factors, willpower, and environmental inputs. Although it is difficult to define the concept of willpower, phenomenologically it is possible to describe what one means in using such a term. When it comes to appetites (or drives) such as hunger, thirst, pain, the need for sleep, or sex, biologic regulatory systems exist which may cause an individual to experience desires to satisfy those hungers which cannot invariably be successfully resisted by means of willpower alone.

Although this chapter has stressed the application of laboratory procedures, it is possible to provide antiandrogenic medication treatment to any interested man experiencing difficulty controlling his sexual behavior through willpower alone, even without performing the tests in question and even if he shows no evidence of a biologic abnormality. Clinical experience suggests that when this form of medication treatment is given to cooperative patients in conjunction with regularly scheduled maintenance group therapy sessions by a well trained caring staff, treatment success is frequently possible. Furthermore, in many instances, this appears to be a just and humane course to follow.

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