A MODEL OF THE EFFECTS OF INTRINSIC, STIMULUS, SENSORY, AND HORMONAL VARIABLES ON THE SEXUAL BEHAVIOR AND RELATED PENILE CONDITION AND SYSTEMIC PLASMA HORMONE LEVELS OF THE MALE RAT

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ABSTRACT

A MODEL OF THE EFFECTS OF INTRINSIC, STIMULUS, SENSORY, AND HORMONAL VARIABLES ON THE SEXUAL BEHAVIOR AND RELATED PENILE CONDITION AND SYSTEMIC PLASMA HORMONE LEVELS OF THE MALE RAT

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A comprehensive organization of the effects on male sexual behavior was developed to describe the empirical state of that behavioral knowledge, to coalesce the complex of male sexual behavior measures, and to reflect on the limits of the current theoretic. The empirical model contains calculated mathematical or logical relationships between the intrinsic, stimulus, sensory, and hormone treatment variables and the behavioral, penile, or plasma hormone variables. The model responds to any combination of the 112 treatment variables and provides values for eight behavioral measures (IL, IF, EL, PEI, EF, PE, PI, PM) and the associated two penile measures (papillae & weight) and three serum hormone concentrations (T, LH, FSH). A rank index of the data based reliability of each output for each behavioral measure is included.

Comparison across the various treatment effects demonstrated consistent relationships between current theoretical mechanisms and the behavioral measures, especially within variable classes. The theoretical copulatory mechanisms were reflected in the IF and EL, the arousal mechanism in the ML, IL, and PEI, and the satiety mechanism by the EF and PE.

Most of the behavioral measures correlated significantly with one another. The IL, EL, and PEI were positively correlated, and the EF correlated negatively. The IF and the PE-PI did not correlate well with

the others, but the IF was the most stable measure and the PE-PI was the most sensitive, reflecting sexual behavior only as a whole. A composite measure of male sexual behavior remains a possibility, but the correlations and consistency among the treatment variable effects was not strong enough to establish clear mathematical relations.

A survey of the effects of the treatment variables indicated the need for additional theoretical constructs: a sensory integrator, a penile component, and hormonal state elements. The sensory integrator had both quantitative and qualitative stimulus and sensory organ aspects. The penile component was strongly dependent on androgens for its prominent support of copulation. The hormones acting primarily on peripheral tissues, like DHT, maintained the operation of copulatory but not arousal mechanisms; hormones acting centrally, like estradiol, maintained arousal and not the copulatory mechanisms.

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TABLE OF CONTENTS

Table of Contents (cont'd) Page

Table of Contents (cont'd) Page

LIST OF TABLES

List of Tables (cont'd)

LIST OF FIGURES

Chapter 1

Introduction

Models are not new to animal behavior, nor specifically to the sexual behavior of the male rat. In the past, Beach (21) postulated two control mechanisms for male sexual behavior, a sexual arousal mechanism (SAM), initiating and reinitiating mounts and intromission, and a copulatory mechanism. The copulatory mechanism takes over with the attainment of an intromission. Consecutive intromissions serve to either cumulatively increase the copulatory excitation to an ejaculatory threshold level (quantal) or maintain a level of excitation over a period of time necessary for ejaculation to occur (temporal). Both the quantal and temporal theories have support (172). Sachs and Barfield (172) have refined these ideas to include changes in the copulatory excitation due to extended intervals between intromissions and have included an inhibitory process following ejaculation. All these concepts are the bases for computer models constructed by Freeman and McFarland (78) and Toates and O'Rourke (197), which produce overt sexual behavior output responses similar to those of an experimental rat group.

Although the theory can partially explain the changes in sexual behavior under normal experimental testing, the assumed "arousal" mechanism, postulated as a change in some central nervous system (CNS) activity, has not yet been anatomically or physiologically demonstrated. Because the concommitant CNS changes cannot be empirically defined, the arousal conceptualization has gained few

adherents. However, no other theoretical controlling mechanisms have been postulated.

A major shortcoming to the sexual behavior theory is its confinement to normal sexual behavior. It is not immediately adaptable to the explanation of changes in behavior due to the influence of the variety of experimental variables altering sexual behavior. The influence of hormonal, sensory, stimulus, and behavioral variables are continually affecting the behavior under nonexperimental conditions but are controlled under experimental conditions. The effects of these variables have no direct input to the current theory or models. No theory of the mechanisms controlling sexual behavior will be adequate until the influences of the impinging variables can be incorporated. Because of this limitation, the computer models based on the arousal-copulatory mechanism also do not allow for the surrounding variables.

Therefore, to bypass the controversial arousal mechanism and incorporate the variables surrounding sexual behavior, an "empirical" computer model was developed. The "empirical" type model was developed directly from a large data base, that was available for the sexual behavior of the male rat, but which was available for few other behaviors or species. The data base was condensed and analysed to defined mathematical and logical relationships between each experimental variable and sexual behavior measure. The relationship between the dosage of testosterone injected over a period of days and the time to attain the first intromission (IL) was an example. These defined relationships were then linked into a whole, relating all intrinsic, sensory, stimulus, and hormonal variables to each male

sexual behavior variable.

The empirical approach stands at the opposite extreme from a purely theoretical model, like the recent computer models of sexual behavior. While the theoretical model assumes underlying principles, the empirical model only simulates the activity of the phenomenon, assuming nothing beyond the experimental data. The empirical approach basically assumes a "black box" between treatment and response, input and output. With sexual behavior, the black box is primarily the CNS. The theoretical model assumes basic structures within the black box, based on hypothesis or theory of controlling mechanism(s). The CNS, in this case, takes on defined functional operating structures, although not necessarily like the anatomical or physiological structure of the CNS.

An empirical model is more descriptive than explanatory. Therefore, it serves mainly as the first stage toward the development and testing of new or improved theoretical models or points directions for future research. As a first stage, the empirical models have limitations, the same limitations as the available body of research. In the case of male rat sexual behavior, the most noticeable limitation is the scarcity of information on interactions among experimental variables. The data are primarily those of the effect of experimental treatments of one variable upon the sexual responses represented by the several male behavioral measures. The interaction limitation calls for the simplest model structure. Therefore, the null hypothesis of no interaction (unless an interaction was defined in the experimental literature) was assumed. However, this was not a presumption of no interaction. Interactions

would be expected, especially among closely related variables, such as between two sensory variables. But when no patterns of inter-relationship are available, parsimony is recommended.

The nearly one hundred variables affecting sexual behavior and the immediate lack of a theoretic incorporating these variables required the tool of a computer. The volume and complexity of the relationships could not be handled intelligibly by linguistic or diagrammatic means. The concise math/logic structure utilized with computers serves well. Hopefully, this organized body of relationships can serve to point out interactions requiring further study and provide the behavioral patterns that components of future models should incorporate.

> '...the model can serve as a valuable integrating framework for behavioral data and as a guide for underlying physiological mechanisms.' (Sachs & Barfield (172), p. 147)

In recent years, male rodent sexual behavior has been studied with waning fervor. This in large part may be due to the complexity of male behavior compared with the more unitary female sexual behavior. The male complex includes several measures of the frequency of response events and the temporal patterning of these events. No single measure emerges preeminent. Confusion persists in interpreting the importance to male sexual behavior, in its entirety, of differential changes in the measures under different experimental conditions. That a particular variable may change one measure and not others further confuses the picture. Unquestionably, a singly, composite male measure responsive to a potential change in any of the

measures in current usage would simplify interpretation of effects and facilitate comparisons of male and female behavioral response.

The possibility of a composite male measure can be assessed when the response of the multiple measures of sexual behavior can be observed over a variety of treatment variables. A wide range of variables is recommended, because each variable or class of variables (e.g., intrinsic, sensory, hormonal, etc.) could differentially affect each measure. To talk about male behavior as a single entity requires the establishment of consistent patterns of change for any treatment, not a new set of patterns, for particular variables or class of variables. For example, the intromission frequency (IF) is often unaffected when others, such as the intromission latency (IL), are altered (172). Potentially some male measures are redundant and those remaining could be associated into a mathematical composite.

On the whole, an empirical model of male sexual behavior can serve two main functions. Standing by itself, it serves as a descriptive reservoir of the known effects of the hormonal, sensory, stimulus, behavioral, and intrinsic variables, that are represented by defined patterns of relationship. Secondly, it serves as a substrate for the development of theoretical models that help eludicate underlying functional principles and for the assessment of the interrelationship of the sexual behavioral measures.

Chapter 2

Behavioral and Testing Parameters

2.1 The Organization of Male Rat Sexual Behavior

The experimental measures of sexual behavior in the male rat are a combination of frequencies and latencies, of event and time. The mount, intromission, and ejaculation are the event measures. These events are organized hierarchically. A mount occurs when the male rises behind the female and grabs her by both flanks, following with palpitation of the female's flanks and pelvic thrusting. The female responds with a curvature of the back, lordosis, and deflection of her tail to the side. An intromission occurs when the penis is inserted into the partner's vagina during the mounting sequence. The intromission is observationally recognized by a characteristic dismount; the male jumps back from the female at the conclusion of the intromission, and usually grooms his genital area. Mounts and intromissions are intermingled during ongoing sexual behavior, although mounts tend to be more frequent earlier in the behavioral sequence.

An ejaculation completes a series of mounts and intomissions. The ejaculation behavior pattern is recognized when the male rises above the female's back with outspread forepaws. The male does not exhibit the dismount characteristic of intromission after vaginal insertion.

Each higher level event in the behavioral hierarchy adds

element(s) to a lower level event. The ejaculation requires both elements of mounting and vaginal intromission. The intromission requires the elements of mounting and pelvic thrusting. Each behavioral event builds to the ejaculation, which terminates a sequence of behavioral events (see Figure 2.1).

The frequency measures are the average number of behavioral events occurring prior to ejaculation. The mount frequency (MF) is the average number of mounts prior to ejaculation for a group of males. Similarly, the intromission frequency (IF) is the average number of intromissions over the same period. The ejaculation frequency (EF) is the average number of ejaculations for a group of males over the entire period of testing.

The latency measures are defined by the occurrence of the behavioral events within a time continuum. Latencies are usually expressed to the nearest second. The first latency measure encountered in the temporal sequence is the mount latency (ML), the time from the introduction of the female at the beginning of the sexual behavior test to the occurrence of the first mount. Similarly, the intromission latency (IL) is the time from female introduction to the first intromission (Figure 2.1).

The ejaculatory latency (EL) immediately follows the intromission latency. The EL measures the time from the first intromission of an ejaculatory series of mounts and intromissions to the ejaculation. The ejaculatory latency can be divided into intervals between intromissions, and these intervals can be individually measured and averaged to produce the inter-intromission interval (III) measure. An analogous measure to the III is the

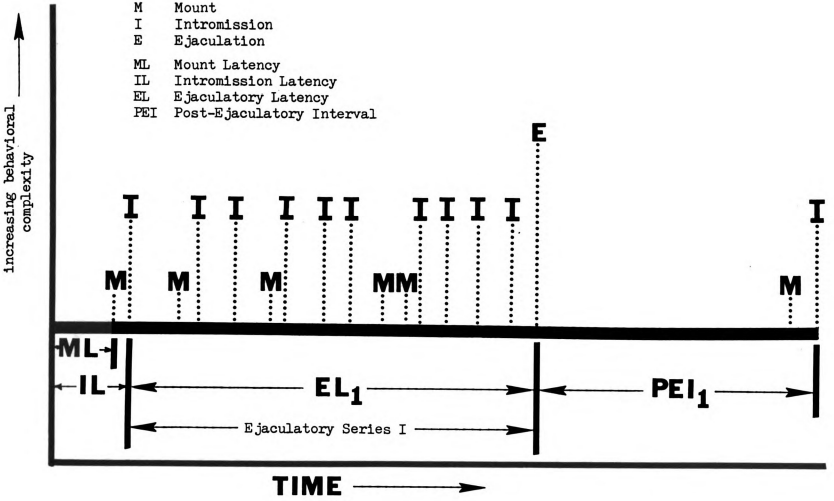

Figure 2.1 THE RELATION OF MALE SEXUAL BEHAVIOR EVENTS AND DURATION MEASURES

inter-copulatory interval (ICI), that is the EL divided by the IF, during the particular EL (ICI = EL/IF).

The final latency measure begins after ejaculation. A behaviorally quiescent period occurs between an ejaculation and the initiation of the next behavioral series of events. The post-ejaculatory interval (PEI) is defined as the time from the ejaculation, terminating one ejaculatory series, to the first intromission of the following ejaculatory series. During this period the male usually lies in a corner of the arena and emits an ultrasonic postejaculatory "song" (2). As the end of the PEI approaches, the male becomes more active and resumes mounting.

The first ejaculatory series, contained within the first EL, is followed by the next ejaculatory series. This sequence is continued repeatedly until the end of testing or the attainment of sexual satiety, the unrestricted termination of sexual behavior. The measures relating to consecutive behavioral series are designated by subscripts appropriate to the order of the ejaculatory series. The first ejaculatory series encompasses MF_1, IF_1, EL_1, and III_1 or ICI_1, followed by PEI_1. After the PEI_1, the second ejaculatory series ensues with MF_2, IF_2, EL_2, and III_2 or ICI_2, followed in turn by PEI_2. This sequence continues to MF_n, IF_n, EL_n, and III_n or ICI_n, with PEI_n. The definition of sexual satiety is generally 15 to 30 minutes without a mount or without an intromission. Otherwise, the behavior test may be terminated at any particular ejaculation or following one PEI.

The more general measures of male sexual behavioral response deal with the number of males in a test group exhibiting mounts,

intromissions, or ejaculation(s). The number of males responding or the percent of males responding is the measure reported in the literature. For modeling purposes, the percent or the number of males responding is converted to a ratio of the number of responding to the total number of males in the group. For example, a ratio of r=0.80 results when four out of five males respond with a mount (PM = 0.80), intromission (PI = 0.80), or ejaculation (PE = 0.80). These measures have the advantage of indicating the degree of nonresponse. The other frequency and latency measures deal only with males that do respond.

2.2 Experimental Testing Parameters

The sexual behavior testing paradigm in the experimental laboratory has substantial variation within the experimental parameters, which serve as a base for all experimental manipulations included in a model of sexual behavior. The factors intrinsically present in any testing situation; such as the rats strain, caging situation, and prior sexual experience; are part of this paradigm. The degree of reporting of the test variables in the literature are discussed here. Particular citations for all parameters are not included as the variables are discussed in more detail with citations in the following chapters.

The intrinsic parameters include the male rat's inbred strain, the housing condition, and the amount of sexual experience allowed prior to the test under consideration. The parameters directly defining the testing situation include: the time during the day the

test occurs, the time or behavioral criteria used to terminate a test, the interval between tests in a testing sequence, the shape and size of the test arena, and the hormonal condition of the sexually receptive stimulus female.

Male Inbred Strain

Four major male strains were reported. These included the Göteborg strain (G); locally reared rats from the Göteborg, Sweden area; Long-Evans (LE), Sprague-Dawley (SD), and Wistar (W) strains. The remaining strains were grouped into a single mixed strain (M) category, because the particular strain was either unspecified within an article or too few articles were available for a particular strain to make any reliable comparisons. The minor strains included the Holtzman, Sherman, CD, and an Israeli strain.

The test male strain reported most often was the Long-Evans (LE). The LE strain was reportedly utilized in 25% of the articles reporting a particular strain. The Sprague-Dawley (SD) strain followed with 18%. The frequencies of the Wistar (W) males (14%) and the Göteborg (G) strain (11%) were less. (The Göteborg percentage did not accurately reflect the hundreds of males used by Larsson (50) in his first book. Only completely different experiments within the book were considered equivalent to one journal publication, and each journal test group usually comprised 6 to 10 males while some Larsson experiments utilized several times that number.) The minor strains (M) comprised a small percentage (7%) of the total and combined with the undesignated mixed strains (25%) produced the total mixed group

comprising 32% of the reporting studies.

Male Housing

Males were housed prior to and during experiments in single or group cages. Of the 130 articles reporting housing conditions, males housed in individual cages (1 male/cage) were the larger category by a small margin (48.5%). The remaining articles reported housed males in male groups (39%) or with females (12%). Males were separated from the females a day or two prior to testing. The average number of males housed together in all male groups was 4.1 $\pm$ 0.3 ($\bar{X} \pm$ SE, N=34 articles), with a range of 1 to 8 males per cage.

When male rats were raised in the laboratory, they were weaned between 14 and 30 days of age. The average age at weaning was 22.6 $\pm$ 0.9 ($\bar{X} \pm$ SE, N=24 studies). The age reported most frequently was 21 days (33%).

Most laboratories had males housed in a room with a controlled light cycle. The Light/Dark 24 hour cycles ranged from 8L:16D to 16L:8D, but most cycles were set to 12L:12D (54% studies) or 14L:10D (35%). THe majority of the light cycles were reversed to facilitate sexual testing during the rat's dark, active period and the experimenter's light period, generally the afternoon.

Prior Sexual Experience

Many male groups had sexual experience prior to testing (73% of the articles reporting the nature of prior sexual experience). Some of the experienced male groups were selected for a definite level of sexual performance (46%). The selection criteria ranged from one intromission to four or more ejaculations. The criterion of one or more ejaculations was the most prevalent (58% of the 59 articles reporting some criterion). The intromission criteria (22% of the articles), the mount criteria (2%), and the test number criteria (19%), regardless of the amount of behavior present in each test ($\geq$ 3 tests), completed the reported options.

Testing Parameters

The testing conditions have several definite parameters. The sexual behavior test takes place at a particular time of day for a defined duration and at set intervals from prior tests in an arena of particular shape and dimensions. The stimulus female is brought into sexual receptivity, usually, through exogenous hormonal stimulation.

Test Time

Because rats are most active during the dark hours, sexual tests were performed during the rat's dark period under dim lighting. Testing occurred usually from 2 to 5 hours beyond the onset of the controlled dark period onward. The average time of test initiation

was 2.9 ± 0.4 (N=26 studies) hours after the lights were extinguished. The mode stood at 4 hours into the dark period.

Duration of Test

The duration of testing was defined by a time limit, a behavioral limit, or a combination of the two. Test times ranged from 3 to 90 minutes. Of the 65 articles reporting a time limit, the average test length was 28.4 ± 2.8 ($\bar{X}$ ± SE) minutes with the most frequent time limits of 15 (23%) and 30 (20%) minutes. Time limits were also counted from the first intromission or mount. These limits ranged from 10 to 60 minutes with a post-intromission average of 20.2 ± 5.1 (N=11 studies) minutes and a post-mount average of 12.5 ± 1.4 (N=4) minutes.

The behavioral limits were a specified number of ejaculations, the termination of a post-ejaculatory interval (PEI) after a specified ejaculatory series, or sexual exhaustion (satiety). In most cases, testing terminated at the first ejaculation or the end of the first PEI (50% of studies reporting behavioral limits). The limit of the second ejaculation or PEI_2 (12%) was much less frequent and limits of 3 to 6 ejaculations or PEI_3 or PEI_4 (8.5%) were inconsequential.

The satiety limits encompassed 24% of the studies reporting behavioral limits. Satiety was defined as 10 to 45 minutes without the occurrence of an intromission or without a mount. The most rigorous definition was 45 minutes without a mount and the most lenient was 10 minutes without an intromission. The average duration without intromission or mount was 24.5 ± 2.0 ($\bar{X}$ ± SE, N=31 studies).

Therefore, of the 209 reported test limits, 31% were time limits

(7% were time limits following the first mount or intromission), 44% were behavioral limits of ejaculation or PEI, and 15% were behavioral satiety limits. The remainder (3%) was the behavioral limit of 2 to 7 intromissions only.

Prior to the initiation of testing, males were allowed an adaptation period in the testing arena. The males were allowed 1 to 15 minutes to acclimatize to the arena. The most frequent adaptation period was 5 minutes (48.5% of studies reporting a period). The average duration reported was 6.8 $\pm$ 0.4 (N=99 studies) minutes.

Testing Intervals

Tests of sexual behavior were usually performed at weekly and bi-weekly intervals. The mode for the number of days between tests (TBT) was seven days (22% of studies reporting TBTs), based on the 166 studies reporting an interval. TBTs of 3 or 4 days (26%) closely followed the mode. The remaining intervals between tests ranged from 1 to 30 days. The average TBT was 5.8 $\pm$ 0.3 ($\bar{X}$ $\pm$ SE, N=182 studies).

Testing Arena

A variety of sexual behavior test arenas were utilized. A compilation of arena shape and dimensions was made (Table 2.1), as these factors restrict the rats' movement to some degree. The arenas were of three basic shapes: rectangular (square), circular, and semi-circular; with at least one transparent side. The floor area was covered with some litter material, e.g., wood chips.

Table 2.1

The Shape and Dimensions of the Rat Sexual Behavior Test Arenas.[a]

Shape	N[b]	Arena Floor Area Mean ± SE cm^2	Arena Floor Area Mean ± SE $(in.^2)$	Arena Floor Area Range cm^2	Arena Floor Area Range $(in.^2)$	Total Reporting Studies
Semi-Circular	34	1878 ± 107	(291 ± 17)	648 - 3283	(100 - 509)	49
Circular	36	3341 ± 278	(518 ± 43)	730 - 5857	(113 - 908)	37
Rectangular	47	2431 ± 461	(377 ± 72)	456 - 22,500	(71 - 3488)	66
Aquaria[c]	6	1155 ± 127	(179 ± 20)	572 - 1372	(89 - 213)	6

Shape	N[b]	Longest Side or Diameter Mean ± SE cm	Longest Side or Diameter Mean ± SE (in.)	Longest Side or Diameter Range cm	Longest Side or Diameter Range (in.)	Total Reporting Studies
Semi-Circular	34	68.1 ± 2.0	(26.8 ± 0.8)	40.6 - 91.4	(16.0 - 36.0)	49
Circular	36	62.9 ± 2.9	(24.8 ± 1.1)	30.5 - 86.4	(12.0 - 34.0)	37
Rectangular	47	50.0 ± 3.0	(19.7 ± 1.2)	24.0 - 150.0	(9.4 - 59.1)	66
Aquaria[c]	6	47.2 ± 1.7	(18.6 ± 0.7)	40.0 - 51.0	(15.8 - 20.1)	6

a -The arena data is based on a total of 158 studies reported in published articles.
b -The total number of studies reporting exact arena dimensions.
c -Comparative information on four-sided glass, 10 gal. aquaria, which are a special case of the rectangular arena.

Several comparisons were possible between the different arena types. The rectangular shaped arenas were predominant (46% of all reported arenas), and the most variable in floor area. The circular arena (31% of arenas) provided the largest floor area and had no corners that block the rats' movement. The semicircular arenas were usually one-half the floor area of the circular arenas, and less than that of the rectangular arenas. However, the semicircular arena provided a larger viewing front (68.1 cm) than the long viewing side of the rectangular arena (50.0 cm). In general, a standard arena offered a viewing, front side approximately two feet in width, but its depth varied, and had a wood chip covered floor.

Stimulus Females

A sexually receptive female is required for optimal male behavior. The receptive female will display full lordosis - arching of the back, raising of the head, and lateral flexion of the tail - in response to a mount, and proceptive or solicitation behaviors, such as ear wiggling and hopping and darting movements, prior to the male's approach and mount.

The experimental test females included intact females on their day of estrus and ovariectomized females given exogenous hormone replacement. The preferred replacement treatment was estrogen given two days prior to the test and progesterone a few hours before testing. However, estrogen alone was frequently used (see Table 2.2).

In the hormone treatment conditions reported in various

Table 2.2

The Frequency and Percentage of Studies Utilizing Various Estrogen Treatments With or Without Progesterone.

Treatments		Prog. N	Prog. (%)	No Prog. N	No Prog. (%)	Total N
Specified Dosages:	EB - 1 dose	67	(48.2)	8	(5.8)	75
	2-3 doses	17	(12.2)	6	(4.3)	23
	Other E_2 forms	4	(2.9)	6	(4.3)	10
	E_2 implants	1	(0.7)	8	(5.8)	9
Unspecified Estrogens		19	(13.7)	3	(2.2)	21
	Totals	108	(77.7)	31	(22.3)	139

Table 2.3

The Average Reported Estrogen Dosages With and Without Progesterone.

Treatment Categories		All Studies Mean ± SE	All Studies N	Studies from 1970 to 1977 Mean ± SE	Studies from 1970 to 1977 N
EB + Prog. -	1 dose	132.4 ± 25.5	67	87.7 ± 21.2	38
	2-3 doses	56.2 ± 13.3	17	60.7 ± 26.5	7
	All doses	117.0 ± 20.7	84	83.5 ± 18.4	45
EB alone	All doses	75.1 ± 23.3	14	87.8 ± 40.5	8

articles, the progesterone dosage was far more consistent that the estrogen dosage. Progesterone was injected at a dosage of 0.5 mg (40% of the articles reporting a progesterone dose) or 1.0 mg per female rat (58%). The rare exception was 2.0 mg of progesterone (2.5%). The injections were given at 3 to 6 hours prior to the sexual test. The majority of studies (63%) injected progesterone at 5 or 6 hours prior.

The progesterone injection augmented the effect of estradiol on female receptivity. The injections of estradiol benzoate (EB) or free estradiol (E_2) were given at one, two, or three days prior to testing. The majority of cases (80% of articles reporting an estrogen treatment) used only one injection, which occurred at 30 to 36 hours prior (20%), 48 to 60 hours prior (37%), or 72 to 75 hours prior (23%) to testing. The remaining studies (18%) used EB injections on two different days prior to testing. The only exception was injection on three consecutive days. Most of the two day injection series were at 24 and 48 hours prior to the test.

The dosage of estradiol was highly variable. The dosage ranged from 3 to 1000 ug EB (see Table 2.3). The mean dosage of EB given in a single injection followed by progesterone was 132.4 $\pm$ 25.5 ug (N=67 articles), and the EB dosage given in each of two or three injections followed by progesterone was 56.2 $\pm$ 13.3 ug/day (N=17).

As the high EB dosage average may have been due to the contributions of earlier articles, a compilation of articles published since 1970 was made (Table 2.3). The mean EB dosage since 1970 was 87.7 $\pm$ 21.2 ug/day (N=38) for the single injection and 60.7 $\pm$ 26.5 ug/day (N=7) for the double or triple dose. The post-1970,

single injection dosage showed some decrease compared to the overall average, although little change was seen in the dosage range. No change occurred with two or three injections. The magnitude of the EB dose used by many researchers was curious, as female receptivity can be induced with 1 or 2 ug EB given 24 and 48 hours prior and 0.5 mg or more of progesterone at 6 hours prior to testing.

Occasionally, estradiol was given without progesterone. The average estradiol alone dosage was 75.1 $\pm$ 23.3 ug/day (N=14), whether given on one day or on repeated days. No discernible difference was observed for the daily dosage between the single and multiple day treatments. The dosages with estrogen alone were approximately the same as those for estrogen with progesterone (Table 2.3). Similarly, the dosage average did not differ noticeably when post-1970 studies were compared with all studies.

Estradiol was also delivered subcutaneously, implanted in silastic tubing or in crystalline pellets. The implants supplied a continuous dose of estrogen over several days. This treatment was used to induce constant estrus, so no progesterone was involved (Table 2.2). In some cases (15%), the dosage, expressed in implant tubing lengths, was not specified.

In general, the majority of articles (78%) reported some combination of estrogen and progesterone (Table 2.2). The remainder (22%) reported a variety of treatments utilizing estrogen alone. In either situation, selection of the stimulus female with a vigorous nonexperimental male or at least palpitation for lordosis would have been advantageous. However, only 57 articles (41%) reported any selection for female receptivity.

Synopsis

The sexual behavior test paradigm included variables of two general types: those intrinsic to the male rat and those pertinent to the test. All the variables were present in any test regardless of other additional experimental treatments. The average conditions produced a male rat from one of four major strains, housed singly or in group cages, usually in male groups. All males had some degree of sexual experience, either due to cohabitation with females in housing cages or established by selection tests, usually to the criterion of one or two ejaculations.

The average test variables described a test starting about three hours after lights-off for the duration of approximately 30 minutes or the completion of one ejaculation or one PEI. Tests were given usually once or twice a week. Prior to the introduction of the stimulus female, males were allowed an adaptation period of about 5 minutes in the rectangular or semi-circular test arena. The stimulus female was commonly ovariectomized and given more than 100 ug/day of EB in one injection at one, two, or three days prior to testing, supplemented with 0.5 or 1.0 mg of progesterone at 6 hours prior to testing.

Chapter 3

Equation Generation and Modeling Procedures

3.1 Introduction

The modeling process begins with the establishment of the normal, control male sexual behavior variables and the experimental treatment variables. Each variable provided with reported data must then be condensed into a pattern of response across the reported range of that variable. The pattern is expressed in a mathematical relationship, usually an equation. The variable patterns are linked within the model program according to their reported interactions or an assumption of independence of response. The model program, besides generating behavioral variables for any combination of experimental variables, controls the reset and incrementation of treatment variables, the sequencing of the behavioral and hormonal subprograms, and the generation of a reliability measure for each experimental manipulation.

The pattern of response is given priority in this data-dependent modeling, because the reported statistical assessments are not always adequate. On occasion, a few studies will report no statistical significance for a given treatment, but a consistent pattern of effect may emerge among the studies. For example, four out of five studies might report a decrease in PEI due to electric shock, but none demonstrating statistical significance. The pattern among the studies, however, indicates an effect of shock. A pattern emerging

from the assessment of all relevant data must be incorporated in the model. The relationship between shock and PEI is significant with regard to the model. This lack of statistical significance is a ubiquitous problem for behavioral data, as rather large differences between individuals exist. The high variance makes the discrimination of differences between treatment groups more difficult. Sometimes, the recognition of a potential pattern must override the point to point statistical negation.

The following sections describe the procedures utilized for decisions among data points or data point-study averages and the methodology for equation fitting. The general procedures used for model construction and a delineation of the structure of the model program follow.

3.2 Procedures for Single Data Points

The decision process dealing with single data points requires some explanation. A single data point refers to an Experimental/Control (E/C) group ratio obtained from reported studies. Usually only male group averages are reported, so the single data point is actually based on several rats. At times, only one data point is available from each study of a particular treatment condition, but at other times multiple data points can be obtained from a given study. The decision procedures provide a single model value from a cluster of data points, an average of data points, or a single data point.

Often no pattern is discernible over the range of the

independent treatment variable, although several data points are available. Sometimes, only one data point, usually a reported study average, is available for a treatment variable. In either case, an equation is useless, even a straight line. The only exception is a cluster of points along the range of the variable. An example of such a cluster is the distribution of points that occur when males are injected daily with testosterone ($\geq$ 100 ug/day TP) starting at castration. The data points vary about a horizontal line, the level of normal behavior, indicating no change over time. However, a horizontal line can be effectively treated as a single point, an average of all points along the time variable line.

Average values are not always reliable. Different studies using the same experimental treatment(s) do not always agree. The behavioral or hormonal response is not always in accord between different laboratories. To reduce the variation due to the laboratory situation, each reported data point for the experimental group is divided by the respective point for the control group. The E/C ratio tends to reduce the discrepancies between studies.

Therefore, the ratio demonstrating no effect is 1.0, a "null" ratio. The main problem with the use of ratios occurs where the actual experimental or control value is very low, such as an intromission frequency (IF) of 1.0 when the normal IF is around 10.0. The resulting ratio (r = 0.1) is very low, and when it is averaged with ratios closer to normal (r = 1.0) from other studies, the average will be biased in the direction of the disparate ratio. An exaggerated behavioral value will be produced when the average is used as an element of the model.

To check the degree of bias introduced by a very large or very small ratio, a ratio of the mean of all experimental values from the different studies is divided by the mean of the respective control values. If a noticeable difference exists between the average of ratios and the ratio of averages, the ratio of averages is the preferred choice.

The variability inherent in a behavioral or hormonal measure and the degree of deviation among the reported data are both considerations in determining the reliability of any average ratio. The reported statistical significance in each study may not alone be sufficient. Frequently, the same treatments result in reports of both significance and nonsignificance in different studies. Where statistical conclusions are in conflict, some guidelines need to be set to determine whether a particular treatment is meaningful; i.e., does an actual effect of treatment exist?

The nature of the behavioral or hormonal measure is the first consideration. Given a ratio of 0.90, some measures would demonstrate statistical significance, but other measures would not. This is due in part to the numerical precision of the behavioral or hormonal measure. A PEI value is reported to three or four decimal places, because the number of seconds can be easily measured. An average PEI is around 350.0 seconds. On the other hand, an IF is reported to only one or two decimal places. An IF normal value is usually 7.0 to 12.0. Because of the difference in precision, a ratio of 0.90 is given more credence if it is a PEI ratio than if it is an IF ratio. The 0.90 ratio is more likely to be statistically significant ($P<.05$) when compared to the null ratio ($r=1.0$) as PEI

than as an IF ratio.

The amount of variation among the studies is also worthy of consideration. The variation can be represented by the direction of deviations of the experimental/control ratios from the null ratio and the reported statistical significance, which is dependent on the variance within each study.

The direction of deviation is the more gross guideline. Obviously, if all available studies report data yielding ratios deviating from r=1.0 all in the same direction, the consistency of the treatment effect is meaningful (Figure 3.1a). This is true even if all ratios are statistically nonsignificant. The average ratio is incorporated in the model when the direction criterion is met. When studies yield ratios above and below the null ratio, the reported statistical significance is considered.

Statistical significance in a majority of studies (Figure 3.1c) requires the incorporation of the average ratio into the model due to its assumed reliability. The rare exception to this guideline is the occurrence of significance on both sides of the null ratio (Figure 3.1e). No effect is assumed here and an r=1.0 is incorporated.

If the studies reporting statistical nonsignificance are in the majority, both the degree of deviation and the direction of deviation from the 1.0 ratio are weighed. In general, a combination of calculated E/C ratios above and below 1.0 require the assumption of no effect and the incorporation of r=1.0 (Figure 3.1b). However, when the direction of deviation of the ratios is weighted in one direction, such as four studies below 1.0 and one above (Figure 3.1c), and at least one study ratio in the directional majority is

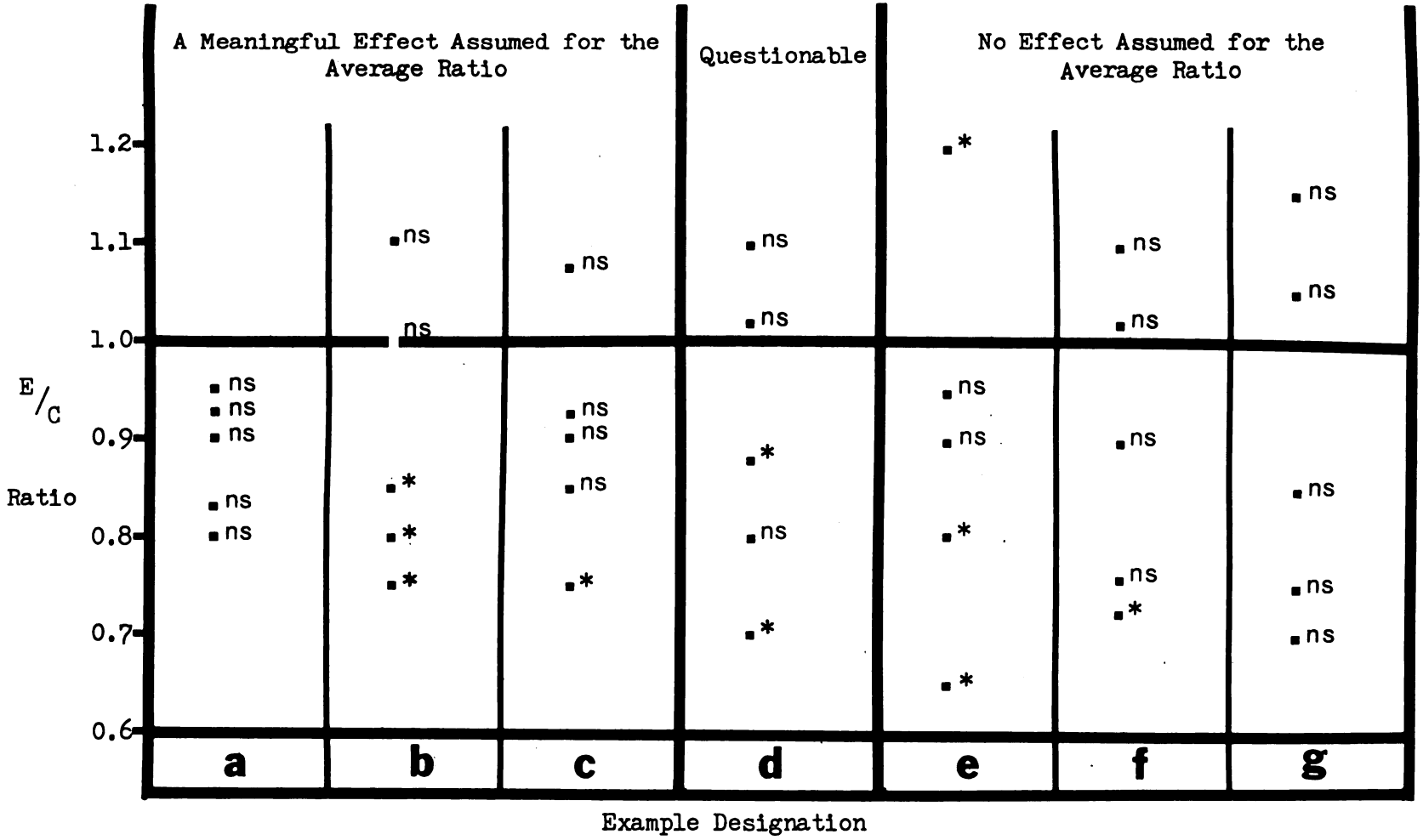

Figure 3.1 Several Possible Distributions of Five E/C Ratio Points with Reported Statistical Significance. The divisions represent decision categories demonstrating the meaningfulness of of the five point distributions. All the groups of points averaged to an E/C ratio of 0.90. (ns - a study point reported as statistically nonsignificant; * - points reported with $p < .05$)

statistically significant, the average ratio is assumed meaningful and the average is incorporated.

When only one study ratio is available for a particular treatment, the statistical significance is followed. The significant ratio from the one study is incorporated as generated from the reported data. Otherwise, the nonsignificant ratio (r=1.0) is incorporated in the model. On rare occasions when a single study ratio is nonsignificant, but due to its large deviation from 1.0 and/or a small number of experimental or control males, the ratio is incorporated as is, since the change from controls is potentially meaningful.

The guidelines mentioned have referred to one point-ratio and averages of point-ratios, where one point is calculated per study. However, often articles report more than one experiment, providing more than one calculated ratio for each article and experimental treatment. If some doubt still persists concerning the reliability of the one point-ratio per study average, the average of all possible ratios is calculated. If the two overall averages closely agree, the one ratio per study average is incorporated. If the multiple ratio per study average is closer to the null ratio, it is chosen. However, if doubt continues, the mean of the multiple and single ratio per study average is incorporated in the model.

All decisions cannot be defined strictly, as indicated by the above guidelines (Figure 3.1). A gray area exists between a meaningful and an inconsequential average ratio, lending the modeler some discretion. The modeler's judgement is aided to a degree by close association with the variability and the limits to that

variability inherent in each behavioral or hormonal measure and between different experimental treatments.

3.3 Equation Procedures

When published studies provide multiple points for each treatment variable, a simple average of the study effects is insufficient. Usually a pattern emerges over the variable's continuum. For most behaviors and particularly for sexual behavior, the continuum is a time variable, such as repeated tests or days of treatment. The pattern can be expressed most concisely by a mathematical expression, an equation. The equation is derived by adjusting a standard equation form to fit the reported data. The shape of the standard form is chosen based on a graphic plot of the data from a single study or the average of multiple studies. The entire process includes the choice of standard equation forms, the preparation of the available data into one pattern, and the fitting of the standard equation form to the composite data.

A choice of equation forms is given in Appendix B. Approximately fifteen general forms are given. The functions include a straight line, square roots, logarithms, exponentials, functions of "e", and sigmoid forms. Most behavioral data could be effectively approximated by variations of a sigmoid curve. However, many patterns of behavioral response do not closely fit the standard sigmoid curve, which has the same rate of change on either side of its midpoint. The behavioral response often shows an initial rapid change that then slowly tapers off to a plateau level. Due to the pattern (curve)

frequent asymmetry, functions of "e" often fit the data better than the sigmoid curve. Therefore, the majority of model equations take an "e" function form. Before the equation choice is made, however, the reported data must be organized and condensed.

The Preparation of Data for Equation Fit

As the control levels of behavioral or hormonal measures varied from study to study, the experimental/control (E/C) group ratio was calculated for each value of the treatment variable for each study under consideration. This produced a number of data point-ratios along the range of the variable's continuum.

However, when no control group value was provided, ratios were calculated based on an average value of all data reported within the study. This was particularly the case for intrinsic variables; such as age (A), strain (ST), time of testing (TDN), time of year (YMON), and light cycle (LTPER). In addition, when too few points were available to obtain a meaningful average, the control value was assumed to be the control value reported by the model for the conditions of the particular experiment, or the control value was the average of control groups from articles originating from the same laboratory using the same strain.

The selection of the appropriate standard equation form was made by visual inspection of a graphic plot of the ratio data. The more obvious tendencies in the data helped to eliminate most of the standard curve forms. Whether the data pattern increased or decreased over increasing values of the treatment variable, or

whether the curve accelerated, decelerated, or was linear was easily spotted when compared with plots of the standard curves. The standard curve(s) most closely following the data pattern were then used for the calculation of fit.

Data Averaging and Adjustment

When more than one study reported three or more data points over the range of the treatment variable (three points are necessary to define a curve), an average curve was sought. An average E/C ratio was generated for each value of the treatment variable reported among all studies. If no value was reported in one study that was in another, an estimated value was calculated.

To estimate a value, a ratio value above and below the missing treatment value was required. The estimated value was established by a linear approximation. In essence, a line was drawn between the two reported values adjacent to the missing one, and the missing value was found at the intersection of the line and the experimental treatment value. For example, in Table 3.1, study number 1 had no treatment ratio values for 7, 21, 35, 49, 56 and 63 days after castration (CAST). These values were estimated (in parentheses). The estimated values between 42 and 70 days post-castration fell on a straight line between r = 0.994 and r = 2.524, respectively. The estimates were found based on the line: r = .05464(CAST-42.) + 0.994.

The combination of estimates and actual values provided an equal weighting for the average ratio for each value of the treatment variable reported. The series of average ratios provided a single

Table 3.1

A Sample Calculation of a Multiple Study Average for the Effect of Castration on the PEI Ratio.

CAST[b]	Individual Study Data[a] 1	2	3	4	Mean	Adj. Mean [d]
7	(1.070)[c]	1.46	1.007	(1.071)	1.152	-
14	1.139	1.50	1.143	(1.217)	1.250	-
21	(1.072)	1.58	1.086	1.300	1.260	-
28	1.004	1.76	1.214	2.087	1.516	-
35	(0.999)	1.82	1.100	1.766	1.421	-
42	0.994		1.186		1.090	1.476
49	(1.376		1.479		1.428	1.934
56	(1.759)		1.564		1.662	2.250
63	(2.142)		1.436		1.789	2.422
70	2.524		1.971		2.248	3.043

[a] The studies included: 1) Whalen and Luttge, 1971 - SD (205)
2) Parrott, 1975 - SD (160)
3) Davidson, 1966 - LE (58)
4) Vomachka, 1976 - LE (198)

[b] CAST is the number of days postcastration.

[c] All parentheses mark data points calculated by linear extrapolation from reported data points.

[d] The final equation fit to the adjusted mean was:

$$PEI_r = 1.0 * e^{-0.01565 * CAST}$$

pattern (curve) to be used for equation fitting.

On occasion, adjustments to the average set of points were necessary when the ranges of the treatment variable did not closely overlap among the reporting studies. Separate values could not be estimated outside the reported variable's range. Therefore, when fewer and fewer studies provided values, due to the approach to the extremes of the variables range, the average curve would become more biased. To counter the bias, the average values of the studies with the wider range were adjusted according to the relative contribution of the studies of larger range. An adjustment was made when at least one study range was exceeded on the basis of the contribution of the other studies when all the studies were within each other's treatment range. The adjustment was the average of all study values divided by the average of the values from the studies with the larger treatment variable range.

$$\text{adj. } r = {}^{\text{Total } \overline{X}_{(n-1)}}/_{\overline{X}_{(n-1)}} \quad \text{for pts with values at "n".}$$

This <u>compensatory ratio</u> was calculated at the last treatment value before the range of any study was exceeded and then multiplied by the average value just outside the range of the overpassed study.

For example, the range of study 2 and 4 in Table 3.1 was exceeded beyond 35 days post-castration. The compensatory ratio used to produce the adjusted mean ratio at point "n" (CAST=42) in the series of treatment values (CAST) was the total mean at the "n-1" value (i.e., at CAST=35, r=1.421) divided by the mean of the values for studies with reported values at "n", i.e., ratios for studies 1 and 3. The mean for studies 1 and 3 was (0.999 + 1.100)/2 = 1.0495.

Therefore, the compensatory ratio was 1.354 (i.e., 1.421/1.0495). The compensatory ratio was then multiplied by the average for values at CAST=42 (r=1.090) to produce the adjusted mean of 1.476. If the study ranges were exceeded in a staggered fashion, the adjustment process would have been repeated each time the range of a study was surpassed.

This adjustment procedure maintained the pattern established initially by all studies. It maintained the proportional relations among studies after values for some studies were no longer available. The termination of the treatment series may have been due to the defined limits of the experiment, the lack of inclusion of all treatment levels in the publication, or the cessation of behavioral performance.

Accommodation of a Standard Equation to the Condensed Data

After reported data was condensed into one set of values (data points) over the range of the treatment variable, the points - whether from a single study, an average of studies, or an adjusted average - could be fit to an appropriate standard equation form. The standard equation was fitted to the data points by generating an equation coefficient for each data point (value of the treatment variable).

For example in the following equation, the "a" coefficient was

$$r = A(1 - e^{-a(x-z)}) + b$$

sought. The values of "r", usually the E/C ratios, and "x", the

value for the treatment variable, were known. In graphic form the "r and "x" values corresponded to the ordinate and abscissa values.

In Table 3.2, the value of "r" was the ratio of the number of males responding with intromission to the total number of males (PI) and the value of "x" was the number of days of injection with 1000 ug of testosterone propionate (DYTTP). The value of the coefficient, "a", was solved.

A reasonable fit to the data points was assumed when the sequence of "a" values from low to high values of the treatment variable fluctuated randomly around the average of all "a" values. In Table 3.2, the "a" values given in a column - one for each value of the PI and DYTTP - were expected to demonstrate no pattern. The "a" values at low DYTTP values should not have deviated noticeably from the average "a"s at high or middle values of DYTTP. The column with z=0 showed an increasing pattern, while the column with z=1.5 showed no consistent pattern, and the "a" values fluctuated around the average a = 0.1032.

The desired fit was sought by a method of logical approximation. The sequence of "a" values were manipulated by changing other coefficients or constants in the equation in a desired direction based on the pattern of change in the "a" column until an acceptable fit was obtained. It was a method of approximation, not an exact statistical fit. In highly variable systems, a tight statistical fit (curvilinear regression) would frequently produce an equation of greater complexity than would have been warranted to describe the relationship between behavioral (or hormonal) and treatment variables. The state of understanding of behavioral systems has not

Table 3.2

An Example of the Fit of a Standard Equation to Composite Data

The standard equation form, $r = A(1 - e^{-a(x-z)}) + b$, was utilized for the fit to data* for the effect of the repeated injection of 1000 ug TP/day as an adult, after castration at 30 days of age, on the PI. The specific variables were: $\underline{x}$ = DYTTP - the number of days of continuous injection with TP and $\underline{r}$ = PI - the ratio of males showing intromission to the total number of males. The preset equation coefficients included $\underline{A}$ = 1.0 and b = 0.0. The $\underline{z}$ value was manipulated and the $\underline{a}$ exponent was calculated for each value of $\underline{x}$.

DYTTP	PI	z=0.0 a	z=1.0 a	z=2.0 a	z=1.5 a
3	.143	.0513	.0770	.1540	.1027
6	.286	.0560	.0672	.0840	.0747
9	.429	.0622	.0700	.0800	.0747**
12	.714	.1041	.1136	.1250	.1190
15	.786	.1028	.1101	.1186	.1142
18	.857	.1080	.1144	.1216	.1179
21	.929	.1259	.1322	.1392	.1356**
24	.857	.0811	.0846	.0885	.0865
27	.929	.0979	.1017	.1058	.1037
30	1.000	-	-	-	-
	Average	.0877	.0968	.1130	.1032+

* The data were taken from Södersten, 1975 (177) (N=14 males).

** The values designated as outliers.

\+ The chosen equation value for $\underline{a}$ was 0.103, when $\underline{A}$=1.0, b=0.0, and z=1.5 .

yet grown to the extent that complex relationships would be expected between variables.

In Table 3.2, the coefficient available for manipulation was "A" and the available constants were "b" and "z". The values of "A" and "b" were set by the nature of the PI, which ranges between 0 and 1. The maximum PI would be all males responding and the minimum would be no males responding. "A" was the amplitude of the equation, the range of the E/C PI ratios, and the "b" the minimum value. In Table 3.2, "A" equals 1.0, because the highest and lowest "r" ratio values were 1.0 and 0.0, respectively. The value of "b" was zero. Therefore, "z" was the remaining candidate. The "z" designated the point on the abscissa (DYTTP value) where the curve started, or the equation equaled zero. The "z" shifted the curve to the right along the "x" axis when "z" was increased.

In the example, the direction of manipulation was based on the sequence of "a" values. With "A" and "b" foreordained, the value of "z" was initially set at zero (see first "a" column). When z=0, "a" tended to increase over increasing values of DYTTP, a condition of poor fit. Because increasing the value of "z" would result in a larger change in "a" at low values of "x" (DYTTP) than at its higher values, "z" was increased to 1.0 to reduce the increasing "a" pattern. As z=1 did not eliminate the "a" pattern, "z" was further increased to 2.0. This made the DYTTP=3, "a" value a little too high so z=1.5 was tried. The z=1.5 manipulation provided a sequence of "a"s with a reasonable fluctuation about the average a=0.1032. Therefore, the model value for "a" for the PI-DYTTP equation was a=0.103.

Sometimes, the values of "a" would show large fluctuations, so

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the assessment of a reasonable fit became more difficult. The selection of certain "a" values was utilized when large fluctuations occurred. The most deviant "a" values were removed from the sequence of "a"s, as a noticeable outlier would bias the average "a" inordinately. The selection of the values to expurgate was based on the original graphic plot of the condensed data. If an "r" value was a noticeable outlier, i.e., off the visual pattern of plotted points, it was discounted. Similarly, points on the less significant portions of a curve - regions where changes in the coefficient had a lesser effect on the equation values - were sometimes discounted. In the case of a sigmoid curve, points at either tail of the curve has coefficients which have less effect with greater fluctuation and less effect on the shape of the curve than points near the midpoint of the curve, which more tightly define the rate of change controlled by the coefficient.

When the mean of all "a" values was closely matched by the mean of the selected "a" values, the mean with the outliers removed, a reasonable fit was assured. Where the total and selected means did not match well, the selected mean was incorporated in the model equation. If a question existed concerning the representative nature of the selected "a" values, or if the number of selected points was very few (less than 4), an average of the total and selected means was incorporated as a compromise.

The fit for the data in Table 3.2 can be seen in Figure 3.2 in graphic form. As stated before, the best fit for "a", the equation exponent, was 0.103, when z=1.5. Although no strong outliers were present in this example, a test of total and selected "a" means could be demonstrated. The more noticeable outliers were the values

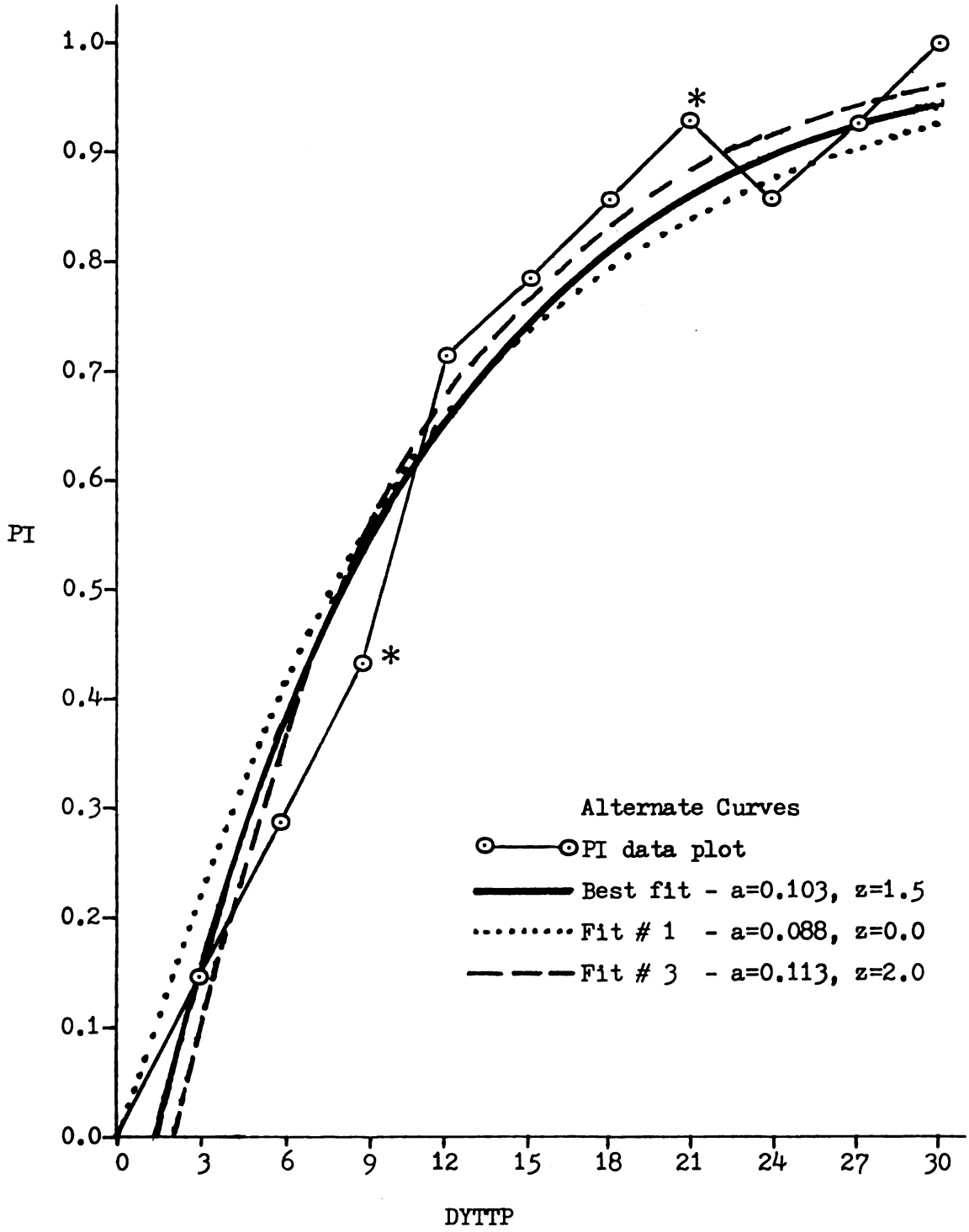

Figure 3.2 Different Fits of Sample Data to a Standard Equation Form. The sample was the relationship of PI data to the DYTTP (days with TP) variable as given in Table 3.2. (* - marks the points designated as the outliers)

at DYTTP = 9 & 21; they were also the highest and lowest values for "a" (Table 3.2). When those two points were eliminated to generate the selected mean, the average became a=0.1027. Because the agreement of the total and selected means was so close, a=0.103 was undoubtedly a proper fit for these data.

When no sequence of "a" values was acceptable, another coefficient or constant in the equation was manipulated. In the equation,

$$r = A \cdot e^{-a(x-z)} + b$$

"A" and "b" were alternates to "z" under some conditions. The manipulation of the "a" sequence with changes in "A" and "b" was frequently useful when the E/C ratios ranged potentially from one to zero. For example, the relationship of the weak androgen, androstenedione, to the ratio of males responding with ejaculation (PE) during a postcastration recovery regime could potentially range from zero to one, but actually the PE rarely grew larger than 0.50. The constant, "b", would again be zero, as the minimum ratio would be zero. The sequence of "a" values over the days of androstenedione injection would have been recalculated. If some pattern was observed in the "a" sequence, the value of "A" could be shifted up or down until the "a" sequence had no consistent pattern.

On occasion, more than one standard equation form was a potential candidate for the data fit. If so, each alternative equation form was used, solving each for the appropriate coefficient, which was usually designated "a". After solving for the "best a" in each case, the fluctuations of the "a" values about the "a"

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average for each equation were compared. The set of "a" values with the least evident deviation from its average determined the equation form to be incorporated in the model.

In summary, the shape of a relationship between a dependent behavioral or hormonal variable (E/C-r) and an independent experimental variable was established graphically. The shape of the relationship determined the standard equation form to be adjusted to the composite data. The opportune coefficient was solved for, with or without the manipulation of other coefficients or constants within the standard. Some of the coefficients and constants were preset by the nature of the variables. When no discernible pattern was observed over the range of the coefficient values appropriate to each experimental average data point, the average coefficient value or some adjustment thereof was considered a reasonable fit. The alternative indication of a reasonable fit was a random fluctuation of coefficient values about its average over the entire sequence of "a" values. The procedure could be extended to more than one standard equation form, which then required a comparison to establish the equation with the minimal variation about the fit.

3.4 Straight Linear Approximations

The straight line was the best option when too few data points were available to discern any consistent relationship, the variance among points was too high to discern a pattern, or a cluster of many points had no definite curvilinear pattern. With very few data points along the range of an experimental variable, a statistical fit

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was no more meaningful than a graphic or visual fit. At times the statistical fit was less meaningful. Sometimes a predictive line was more meaningful when anchored to an expected point or a theoretical point. For example, if a behavior was initially at a zero level prior to the initiation of treatment, the line was best anchored at zero at the zero value of the treatment variable rather than some value greater or less than zero established by a statistical fit of the available data (Figure 3.3).

A straight line was also useful in bridging a region of the range of a treatment variable where no data were available. The straight line was the simplest connector between any two known points or regions. Implicit in the use of a line was the assumption of no particular pattern within an "empty" area.

The procedure for fitting a line to the data was similar to that for the equation-curve. The line was determined from the pattern of the available data and its relation to other data or theoretical points. The graphically represented line could be drawn to connect an anchoring point and a data point, two data points, two average points generated from three points, or to follow the direction of several points, with or without consideration of a theoretical trend (see Figure 3.3). The equation for the line could then be calculated.

The equation for a straight line, $y = a \cdot x + b$, required the calculation of two values; "a", the slope, and "b", the y-intercept. As each point was defined by two coordinates, (x_n,y_n), and any two points $(x_1,y_1$ & $x_2,y_2)$ could be used to define the line, the slope was the difference between the two "y" coordinates divided by

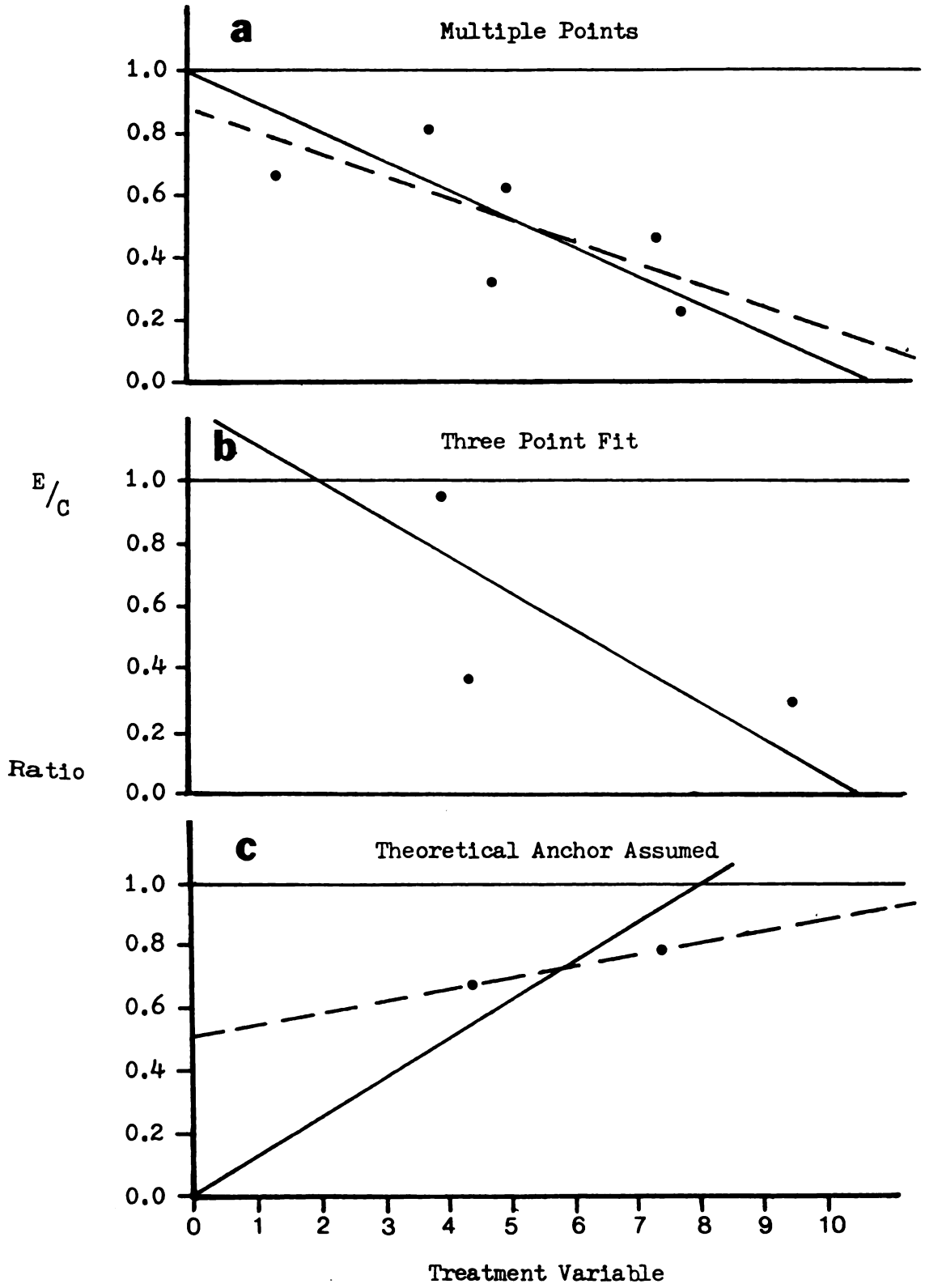

Figure 3.3 Linear Approximations to Three Different Types of Data Point Distributions. (———Model Approximation; — — — Statistical Fit)

the difference between the two "x" coordinates.

$$\text{slope} \quad (a) = {}^{(y_2-y_1)}/_{(x_2-x_1)}$$

Establishing the y-intercept was not as clear. The value of "y" (the E/C ratio) when "x" (treatment value) equalled zero could be read from the graph or calculated if the slope and one point was known. The intercept was usually not found by an exact statistical fit. The intercept, as well as the slope, were often limited by considerations pertaining to the relationship (Figure 3.3a). Aspects of that relationship included an initial control level of 1.0 or 0.0 and relations to data at another part of the variable's range.

Once a graphic line was drawn to relate three or more points, the deviations of each point from the line were found. The deviations were grouped according to those either above or below the line. The sums of the above and below groups were compared. If the sums were not equal, the value of the y-intercept was raised or lowered, keeping the same slope, until the sums of the two groups were approximately equal. When several lines were possible, the line with the lowest Least Square value was placed in the model.

Again, the purpose of these procedures was to find a fit representative of the pattern of response demonstrated in the available literature rather than an exact fit to the particular data points. This approach reduced the possibility of required changes in the model equations due to the addition of data from each new study, changes that would be required each time if the fit were statistical; a more representative line would tend to be consistent with present

and future data. For a high variance system, as sexual behavior is, an exact measurement would provide great precision, but if the addition of each new point required a recalculation of the numerical relationship, the tool would have been too fine for the object measured; the height of an elephant is not measured with calipers.

Chapter 4

Model Structure and Preparation

4.1 The Basic Structure of the Model

The model is composed of fourteen separate units. The basic structure is a backbone, the main program, controlling the operation of the other subprograms, which relates the subprograms calculating behavioral or hormonal output values (eleven in number) and the diagnostic subprogram, which provides a reliability value for the output (see Figure 4.1).

The Main program controls access to all operations. It presets all the input variables, calls the Input subprogram to reset user designated treatment or increment variables, increments all variables for each successive iteration, controls access to the calculation subprograms, and finally calls the diagnostic subprogram. After all treatment and increment variables are preset at the start of the main program, the Input subprogram is called to read in the values for any treatment or increment variable the user wishes to reset. The Main program proceeds to call the calculating subprograms, generating the output values. Communication among the Main and subprograms is through COMMON memory storage. After the output of the behavioral and hormonal measure values and the reliability values generated by the Diagnostic subprogram, control returns to the beginning of the Main program for incrementation of the input values.

The iteration subroutine, when accessed by the Main program,

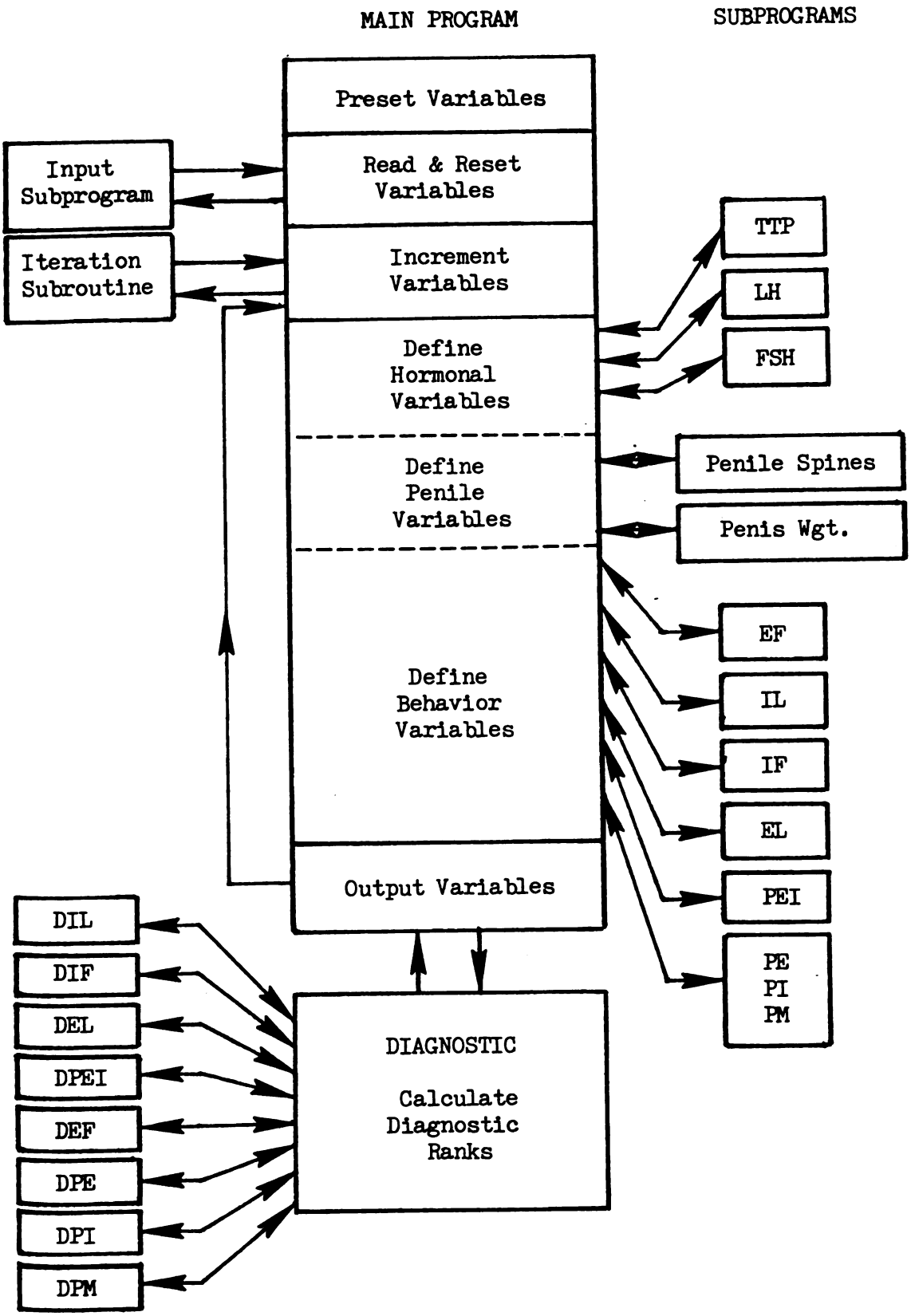

Figure 4.1 The Basic Structure of the Model

increments all input variables with each cycle of the model. Each treatment variable is added to its associated increment variable to reset the treatment variable values for the current cycle of the model. For example, if a male rat's age was set at 200 days by the user and its increment set at 7 days, the first set of output values printed would be for a male of 200 days of age, the second cycle for a male of 207 days of age, out to the fourth cycle at 221 days of age. This number of cycles would be set by the NINC value of 3, the number of iterations. The same process holds for any number of input variables.

The Main program controls the order of access to the hormonal, behavioral, and penile subprograms, and it accepts the output values from those subprograms, storing them for future output in arrays. When all output values are calculated, the program prints a display of the output using a display subroutine. The last activity in a cycle is calling the Diagnostic subprogram, which calculates and outputs reliability values for all output measures.

The calculation subprograms are in the greatest number. Each of these subprograms independently generates its output values, whether behavioral, hormonal, or penile in nature. The only way an output value from one of the subprograms can influence another is through the Main program. The hormonal subprograms generate a normal resting level and an experimental plasma hormone value. The testosterone (T), luteinizing hormone (LH), and follicle stimulating hormone (FSH) units generate their appropriate plasma levels, based on the established treatment variables. The behavioral units generate a control and experimental value for each of the following behavioral

measures: ejaculation frequency (EF), intromission latency (IL), intromission frequency (IF), ejaculatory latency (EL), post-ejaculatory interval (PEI), and the ratio (percent) of males responding with ejaculation, intromission, and mounting (PE PI PM). Each behavioral measure has its own subprogram, with the exception of the ratio-responding measures which are combined into one large unit. Finally, the penile units are two in number. They provide normal and experimental values for the number of penile papillae in a cross section of the glans penis (PP) and for the weight of the whole penis (PW).

The Diagnostic subprogram is a third type of unit. It generates as estimated measure of reliability for each output value, based on the values of the input, treatment variables. It is a repository of the variation across the range of all variables that are input and provides an independent reliability for each output variable through separate subprograms for each of the behavioral measures controlled by a single operational unit. The printing of the values from this subprogram signals the end of the current iteration cycle.

4.2 Modeling Procedures

The construction of each model part, whether a separate subroutine or subprogram, involved developing each unit separately, so they operate as semi-independent units. Each unit was constructed following a few general procedures. The description of the procedures does not require an explanation of the FORTRAN language, which is beyond the scope of this paper. The procedures depend upon

the type of program or subprogram. The major types include the Main program and Input subprogram, the various behavioral and hormonal calculation subprograms, and the Diagnostic subprogram.

Principles for the Main and Input Programs

The Main program and the Input subprogram are the most complex. The Main program establishes an initial value for all input, treatment variables and incremental variables. These variables are listed and described in Appendix A. Initially the values for all variables are established using DATA statements, that set the values for each variable prior to any other activity of the program.

After the variables have been preset, the individual using the program can reset them to define any experimental condition desired. The reset process is handled by the Input subprogram, the first subprogram accessed by the Main program. If the user designates no values, the program generates the output values for a normal adult control male group determined by the preset input variables. the reset process is accomplished through the NAME variable. The user is supplied with a list of NAME designations (alphanumeric characters listed in Appendix A), one available for each input variable. When a value for NAME is designated, the user must follow with a chosen numeric value for the named input variable and its increment variable. This double input procedure may be repeated for as many input variables as desired. When the name variable is given the value of FLAG, the reset process is terminated and control returns to the Main program.

The iteration subroutine is called from the Main program at the end of the cycle. It increments each input variable by the value of its associated increment variable. The Main program then continues from its beginning with the new set of input variable values to recalculate the output variables. The cycling of the Main program continues until the number of iterations set by the NINC variable, the first value set by the user before any NAME variable, is attained. At that point the model ends and all execution is terminated.

When all the values for the input variables are established - either by initial reset process or through the iteration reset process - the Main program proceeds to access the subprograms that calculate the behavioral, hormonal, and penile output variables. All of the 11 output subprograms are called, and the experimental and control output variable values are calculated and returned to the Main program. The values for the input and output variables are communicated through COMMON memory storage.

The Main program controls the order the calculation subprograms are called. The first group called is the hormonal subprograms, which calculate the values for plasma T, LH, and FSH. An injection dosage of testosterone is calculated by the main program based on the plasma level of T, which in turn was determined either by a user designated value (PLT) or through a cyclic feedback with the LH and FSH subprograms. As LH and FSH from the pituitary normally controls the production of T and its consequent level in the blood, their subprograms interact within the Main program until their values are internally consistent. The interaction is accomplished by converting

each plasma level value to an injection dosage, which then is an input variable when the hormone subprograms are recalled. The T subprogram is dependent on changes in the LH and FSH subprograms, and vice versa. When consistent values among the three hormone subprograms are attained, the Main program proceeds.

The second subprogram group is the penile units. The PP and PW subprograms require no special manipulation. They report one set of output variables, one for the penile papillae number and one for penis weight.

The final and major group of subprograms called is the behavioral group. All the behavioral subprograms, except the EF, are embedded in a DO loop to cycle the remaining subprograms through five ejaculatory series plus the consequent PEIs. Therefore, the IL, IF, EL, PEI, and PEPIPM subprograms are called five times in sequence, each time reporting control and experimental values for the appropriate number of the series.

In addition, after calling all calculating subprograms, the Main program calculates ancillary measures of sexual behavior and the E/C calculation subprograms. The first ancillary measure is the intercopulatory interval (ICI), the average interval between intromissions in each ejaculatory series. It is the ejaculatory latency divided by the intromission frequency (EL/IF), calculated for the experimental and control values, independently. The ICIs are followed by the total response measures. The totals represent response averages that occur when both responding and nonresponding males are included together. The total behavior measures allow for comparisons with published data including zero data. As the IL, IF, EL, and PEI model

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values reflect only responding males, the model values are multiplied by the appropriate ratio of males responding (i.e., PE or PI values). The values calculated are:

TOTIL=IL*PI

TOTIF=IF*PI

TOTEL=EL*PE

TOTPEI=PEI*PE

Furthermore, the experimental/control (E/C) ratios are calculated from the two output values from each subprogram. Therefore, ratios are reported for plasma T, LH, and FSH; the EF, IL, IF, EL, PEI, PE, PI, and PM behavioral measures; and the penis weight (PW) and papillae number (PP).

The Display subroutine is called following the completion of all calculations and the loading of all output values in appropriate output arrays. The Display subroutine causes the printing of the separate experimental and control values for the IL, IF, EL, PEI, PE, PI, and PM and the experimental value for the EF on one line. The five consecutive ejaculatory series follow on the next lines. The ancillary behavioral values are given next across the five series; they include the ICI values and the experimental total measures. These are followed by the E/C ratios for the behavioral measures. The hormone and penile experimental values then appear with the number of hormone cycles - the number of times the program needed to loop between the T and LH and FSH subprograms to result in mutually agreeable values. The last values displayed are the E/C ratios for the hormonal and penile measures. The entire display is repeated for each iteration of the program.

The Main program now calls the Diagnostic subprogram, that

calculates and displays reliability values for each behavioral measure over all behavioral series. A more detailed description of the Diagnostic subprogram is given in a later section. When the number of iterations reaches the value of NINC, the Main program terminates.

Calculation Subprogram Procedures

The eleven calculation subprograms include six behavioral units (EF,IL,IF,EL,PEI,PEPIPM), three plasma hormone units (T,LH,FSH), and two penile units (PP,PW). Each of the subprograms is separated into divisions. The multiplication of all experimental effect ratios within each division produces an overall ratio for that division. The multiple of all the divisions produces the experimental output value for the particular subprogram. The control output value is the resulting ratio from the first division, that calculates a value for the effects appropriate to a normal untreated male rat.

The number of divisions is potentially seven. The divisions are for control male (intrinsic) values, experimental and stimulus manipulations, sensory treatments, major gonadal hormone treatments, androgen effects, nongonadal hormone treatments, and drug effects. However, all divisions are not always present in every subprogram. Divisions are combined if few values are calculated for one division, due to a lack of available data or the lack of any experimental effect (i.e., the E/C ratio is 1.0 for a given treatment). Frequently the hormone treatment division is combined with the androgen and/or drug or nongonadal divisions.

The first division, the control measures, contains all the variables required to define a normal male left untreated. The variables include the strain, age, month of the year, light cycle, and time of day. These variables are handled somewhat differently, because the control variables have no actual E/C ratios. They use ratios of the particular condition to the average or normal adult condition. For example, the responsiveness of the male changes during the dark period, so a TDN value on either side of 5 hours, the approximate time of most testing, into the dark period would be a ratio of the response at the particular TDN value to that at 5 hours. All variable ratios are in turn multiplied by the average response across all control groups for the subprogram measure.

The experimental division is a less distinct collection of variables. It contains variables that attempt to manipulate the males; behavior and conditions relevant to the testing situation. The test variables include the time between repeated tests (TBT), the males' prior sexual experience (a normal male is assumed to be completely experienced), and the caging situation. The behavioral manipulation variables include enforced ICI's and PEI's, the receptivity of the female partner, female exchanges, electric shock, positive and negative conditioning paradigms, and other miscellaneous manipulations, such as testing males and females in groups or use of collars to prevent genital grooming.

The gonadal hormone division contains castration, cryptorchidectomy, and injections of testosterone or estrogen in various forms. The androgen division contains calculations for the remaining androgens. These include dihydrotestosterone (DHT), androsterone,

androstenediol, androstenedione, androstanediol, androstanedione, and hydroxytestosterone in various forms.

The following division is a miscellaneous nongonadal hormone treatment category, and it is usually attached to another division. It includes the surgical removal of the hypothalamus, adrenal glands, thyroid, or pineal gland. Furthermore, injections of LH and/or FSH, human chorionic gonadotropin (HCG), and forms of progesterone, prolactin, and pregnenolone are contained within.

The final division holds anti-androgen and anti-estrogen drugs of various modes of action. Included are androgen mimics such as fluoxymesterone, anti-estrogens such as MER-25, anti-androgens such as cyproterone acetate (CYA) and flutamide (FL), and aromatase inhibitors such as aminoglutethimide (AGT). Also, effects of starvation are tacked on at the end.

Information moves between the calculation subprograms and the Main program through shared COMMON memory. The output variables, an experimental and control value from each subprogram, are transferred through a separate COMMON block.

Several general principles are in operation in each of the calculation subprograms. The organization of the subprograms is essentially linear. The progression of calculation moves from the beginning to the end of the subprogram, each division and each variable within the division, in sequence. Basically, no internal loops, no returns to earlier calculations, are present.

Calculations for an input variable are skipped if the value of that variable has not been changed from its preset value, usually zero. For example, the equation for the number of males responding

in the PEPIPM subprogram to a dosage of testosterone is bypassed unless the value for the input variable, DTTP, is greater than zero. The unrequired equations and variable values are bypassed with IF statements.

Limits are set for all calculations exceeding a theoretical value or exceed maximum or minimum values inherent in the averaged data. The limits are frequently required to prevent continuous extrapolations beyond the data supported variable ranges. For example, an equation for a straight line would generate solutions larger than 1.0 for some elements of the PEPIPM subprogram, and as more than 100% (r=1.0) of the males cannot respond, a maximum limit is necessary. The limits are established with IF statements also.

Access to some treatment ratio values or equations is controlled with controller variables. These integer variables provide the user with a list of different related experimental treatments, each treatment having a whole number designation (descriptions in Appendix A). For example, NFRESH is a controller variable with four possible treatments pertaining to when a female partner is switched during a sexual behavior test. If the switch was to be made at each ejaculation, NFRESH would be set at one (1), and at ten (10) if the switch occurs only at sexual satiety. Logical IF statements serve to test for the value given the controller variable, and with the appropriate value allow access to the value or equation for the E/C ratio for the particular variable and output measure.

After the various program instructions have been followed to produce a number of treatment ratios, these ratios within each division are multiplied together, producing a division ratio. The

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division ratios are multiplied together to form the overall experimental output ratio. When the overall experimental ratio is multiplied by the control output variable, the value from the normal control division, the experimental output variable emerges. If only a male stimulus object treatment (SEXSTIM=10) is desired, the experimental division and overall experimental ratio for the IF subprogram would be 0.50. If the normal control variable value was CIF = 10.0, the experimental output variable would have been IF = 5.0 when the experimental ratio is multipled by the control value.

4.3 Diagnostic Preparation

The diagnostic portion of the model provides a measure of the relative reliability for the behavioral output. The reliability is expressed as a rank from 0 to 10. Each rank is based on the amount of data and the variability within the data available. The rank values do change over the range of each input variable and over the five consecutive ejaculatory series. The eight behavioral outputs (IL,IF,EL,PEI,EF,PE,PI,PM) are treated independently with regard to the generation of ranks, so the ranks can vary from measure to measure for the same input variable. The average rank, minimal rank, and the midpoint between the two are reported as a second output section.

The Diagnostic subprogram is called by the main program after the calculation of the output variables. The Diagnostic subprogram calls the rank generating subprograms, one for each behavioral measure. Each reports one rank for each input variable designated by

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the user to the calculation subroutines. The subroutines generate the average and minimal rank for all designated input variables. The Diagnostic subprogram displays and stores the final ranks as a matrix and reports the ranks, one for each output measure and each ejaculatory series, for each cycle of the total model.

Diagnostics are provided for the behavioral variables only. The hormonal (T,LH,FSH) and penile (papillae and weight) variables are not provided with reliability values as these variables hold a secondary position within the model. The plasma hormone and penile output measures provide information on the concurrent condition of the hormonal system and penile structure, which only indirectly influence the generation of the behavioral output. The behavioral responses are the primary focus of the model, so behavioral reliability measures are deemed sufficient.

The following sections describe the exact procedures required to generate the diagnostic ranks and the general structure of the diagnostic programming. The measures of the data reliability used for the generation of the diagnostic ranks follow immediately.

Calculation of the Reliability Measures

Six numerical measures provided the basis for the reliability of the behavioral response to the input variables. Reliability measures were developed for each input variable for each of the behavioral output variables. Three measures provided information about the variability within the available data and three measures described the amount of data available.

The variability measures were statistical. The deviations of all reported data points from the model value were found. Several deviation values could occur over the range of a single input variable. These deviations were found for all input variables for each behavioral output measure.

For example, the relationship of the input variable, CAST (the number of days after castration), to the output variable, EL (ejaculation latency (sec.)), was supported by 15 data points from three studies (59,198,205)(see Figure 4.2). The difference between each data point and the corresponding model value provided a deviation value for each data point at the appropriate value of CAST. At CAST = 56 days the model value was based on the equation:

$$\begin{aligned} \text{CASEL} &= .021(\text{CAST}) + .774 \\ &= .021(56) + .774 = 1.95 \end{aligned}$$

As the actual data point was 1.537 (E/C ratio), the deviation value was the difference, 1.537 - 1.95, of -.413. The remaining 14 points were generated the same way. The statistical measures of variability about the model value(s) made use of the deviation values.

The statistical measures were combinations of the mean, median and standard error. The sum of the mean and the standard error ($\overline{X}$ + SE) gave an indication of the degree of variation surrounding the model value(s). The second measure, the ratio of the standard error to the mean ($SE/\overline{X}$), showed the relative contribution of the SE to the first measure. This ratio required an adjustment to the more limited range of 0.5 to 1.0, because otherwise it has an excessive influence when combined with the other deviation measures. The choice of 0.5

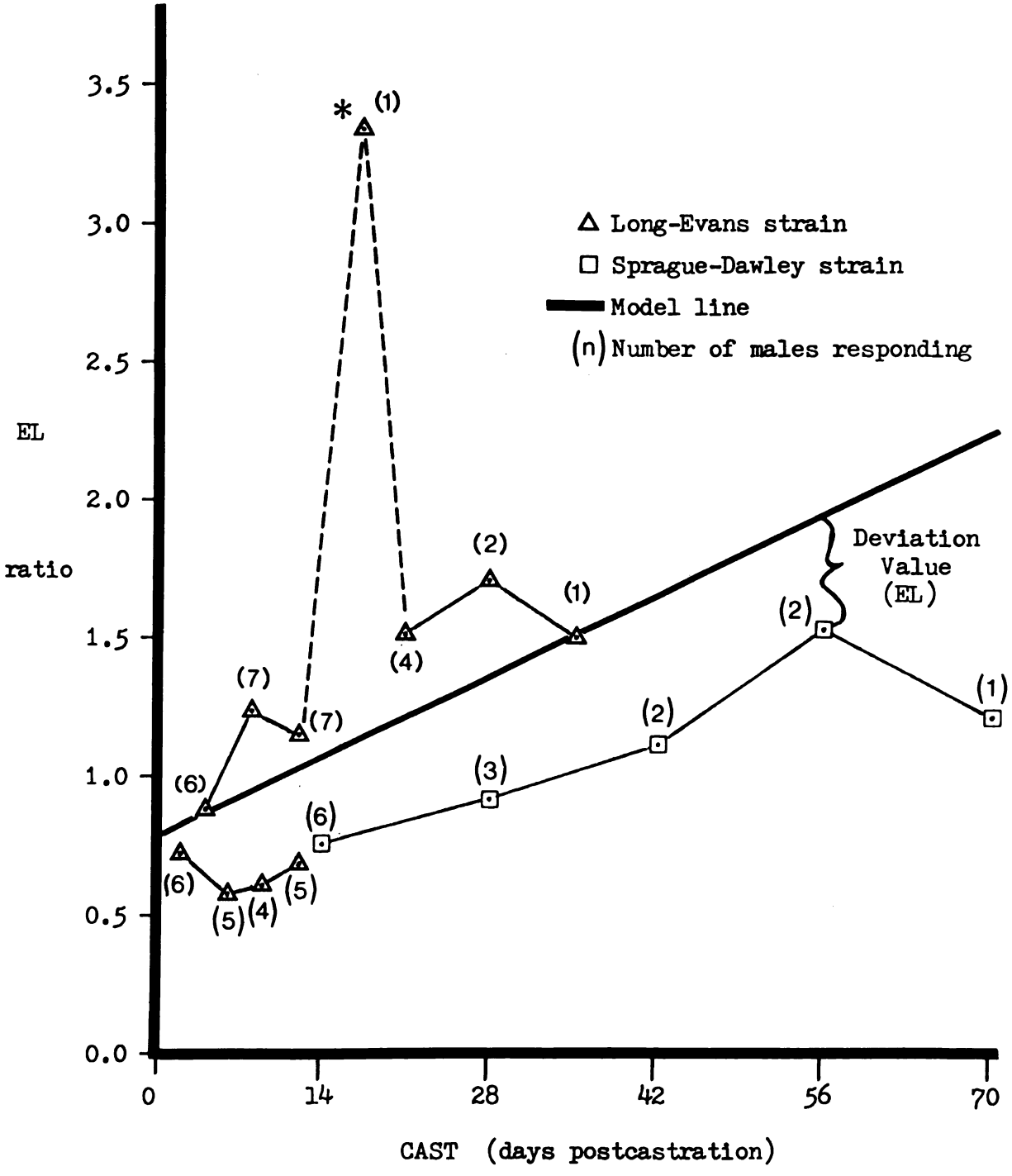

Figure 4.2 The Relationship of Data Points from Three Studies to the Model Values Utilized in the Calculation of Deviation Values. The values are for the relationship of the CAST to the EL ratio variables. (* designates the point not used in the deviation calculations because it was an extreme outlier, representing the response of one male rat.)

as the lower limit was arbitrary. The second measure was generated in the following manner:

$$S_r = 0.5\ (SE/\overline{X}) + 0.5$$

The third statistical measure was the ratio of the median to the mean ($MDN/\overline{X}$). The ratio represented the degree of divergence of the particular set of deviation values from a normal distribution. The greater the divergence from a normal distribution was, the less reliable all the statistical measures were. The $MDN/\overline{X}$ ratio was adjusted so the measure ranges only above the 1.0 ratio for the normal distribution, so the overall reliability is altered in one direction only from the minimum absolute fit. The third measure followed the form:

$$M_r = |MDN/\overline{X} - 1.0| + 1.0$$

The three measures of data quantity were the total number of points (N_p), the total number of studies providing those data points (N_s), and a weighting for the number and type of male rat strain (ST_w). The strain weighting was calculated using:

$$ST_w = \Sigma\,(N_{st})^2/N^2_{study}$$

(where N_{st} was the number of studies utilizing the same strain and N_{study} was the total number of studies involved)

Both the measure for the number of points (N_p) and studies (N_s) required alteration. A factor that increased with decreasing number of points or studies, i.e., decreasing reliability, was needed.

Three studies or three points were chosen as the cut-off value

for decisions concerning the weighting of the study or point factors. One or two studies were frequently inadequate in providing distributions of points for the statistical measures of deviation. The low number of studies tended to underestimate the behavioral variation, because the amount of deviation from the model was based on the methods used to generate the model values or equations. With one or two studies, especially studies from the same laboratory, a closer fit could be provided than if a number of studies were involved. Three data points were chosen because three points were required to indicate whether the relationship was linear or curvilinear. In general, a closer equation fit can be made to a small number of points than to a large number for a variable phenomenon. This had to be adjusted when considering the reliability.

When all deviation measures were viewed and compared, a simple difference factor like (4 - N) was found to be inadequate. Some reasonable measure of reliability needed to be established to counteract the fitting procedure. The requirement that the ranges of the statistical measures of deviation for a single point and/or study not overlap the ranges of the statistical measures for three or more studies and/or points was deemed reasonable. To accommodate this requirement, the factor for studies was established as:

$$N_r = (4 - N_s)^2 \quad \text{for } N_s \leq 3$$

For the factor for number of points, which was considered in low numbers as a stronger measure of unreliability than study number, the difference needed to be doubled and squared to meet the requirement:

$$N_p = (2(3 - N_{points}))^2 \text{ for } N_{points} < 3$$

If the reliability factors for points and studies are combined, the following factor table results:

Table 4.1

Factors For the Total Number of Studies and Points

		N_{points}		
		1	2	3
N_{study}	1	144	36	9
	2		16	4
	3			1

The table effectively counteracted the biases in deviation values induced by the calculation of model equations of values from a small number of points and studies. For example, two points can be fit exactly, i.e., zero deviation, but the resulting reliability measures are not representative of the population of male rats.

When all six measures of reliability were adjusted so they related as multiple factors, providing a single, combined numerical reliability measure (RN). The factors of the combined mean and standard error, N_r, and N_p were stronger factors. Table 4.2 provides a specific case demonstration of the calculation of the six measures and the resultant NR.

When a larger data base was available for a particular variable,

Table 4.2

A Sample Calculation* of the Numerical Reliability Value (NR) From the Six Measures of Reliability.

1) $\bar{X} + SE = 0.331 + 0.06235 = 0.39335$

2) $S_r = (SE/\bar{X})*0.50 + 0.50 = (0.06235/0.331)*0.50 + 0.50 = 0.594$

3) $M_r = \left| Mdn/\bar{X} - 1 \right| + 1.0 = \left| 0.510/0.331 - 1 \right| + 1.0 = 1.5415$

4) $ST_w = \Sigma(N_{st})^2 / N^2_{study} = (2^2 + 1^2)/ 3^2 = 5/9 = 0.556$

5) $N_r = (4 - N_{study})^2 = (4 - 3)^2 = 1.0$

6) $N_p = (2*(3 - N_{pts}))^2$ for $N_{pts} < 3$; with $N_{pts} = 15$, $N_p = 1.0$

$$NR = (\bar{X} + SE) * S_r * M_r * ST_w * N_r * N_p$$

$$= 0.39335*0.594*1.5415*0.556*1.0*1.0 = 0.2003$$

* The example presented is the relationship of the CAST input variable to the EL ratio output variable.

divisions were made within the variable's range. Reliability measures were found within each division and the NR calculated. The division allowed changes in the NR over the range of an input variable. The CAST input variable in the PE (ratio of ejaculating males) output variable provides an example of a variable with divisions.

The CAST - PE relationship was divided into 18 parts, each with an average number of points of 6 (total N = 109). The pattern of the deviation means followed a linear relation represented by:

$$\bar{X}_{PE} = -.002594\ (CAST) + .234,\ 0 \leq \bar{X}_{PE} \leq .205$$

The standard errors showed no discernible pattern over the range CAST, so the average deviation SE was adopted (SE = .03394).

The NR was calculated for the maximal and minimal $\bar{X}$ and SE segment for any divided input variable. The maximum and minimum values for the CAST - PE case were respectively $\bar{X}$ = .205 and .0135 for the segments CAST = 3-5 and 70-85 days.

Because the deviation equations did not fully represent the fluctuation about the equation line, secondary deviations of the segment means or SEs from the deviation line were added. The secondary deviations were generated in the same manner as the primary point deviations. The secondary deviations were added to the primary deviations taken from the deviation line.

$$\text{Tot. } (\bar{X} + SE) = (\Delta\bar{X}_1 + \Delta\bar{X}_2) + (\Delta SE_1 + \Delta SE_2)$$

For the CAST - PE example, the maximum and minimum extremes were as follows:

$$Tot._{max} = (.205 + .0707) + (.0339 + .0163) = .3259$$

$$Tot._{min} = (.0135 + .0707) + (.0339 + .0163) = .1344$$

The remaining five reliability measures were assumed constant over the range of the input variable supported by data. The changes in the RN were, therefore, a reflection of the changes in the deviation mean and SE sum. The segmentation procedure made the variation along the variable's range more comparable with variations for input variables having no ranges such as all the sensory variables and most of the experimental nonhormonal variables.

Generation of the Ranks

After the numerical reliability values were developed for all the input variables for each of the eight behavioral output variables, the RNs had to be converted to ranks to aid user intelligibility and the comparison among output variables. The conversion to reliability ranks occurred in two stages.

During the first stage, the ranks were generated from the RN values and set to range from 0.1 to 9.7. The curtailed range was necessary to separate the deviation values demonstrating variability from those that did not. The zero rank was reserved for input variables with no data or outside the range of the values of an input variable. The 10.0 rank was reserved for deviation values that were all equal over a particular range of the input variable in multiple studies. In almost all cases, the equal deviation values were zero.

These consistent zeros occurred primarily during the early stages of a recovery regime under hormone replacement, where males had stopped responding sexually prior to the start of treatment.

The ranks were established such that a high level of reliability, i.e., little deviation from the model values, was represented by the higher ranks and the low levels of reliability were represented by the low ranks. The reciprocal of the numerical reliability value (NR) was the core of the rank generation.

As the reciprocals (1/NR) ranged from almost zero to approximately one hundred and the ranks were set to range from 0 to 10, the square root of the reciprocal was taken. The adjustment for ranks ranging from 0.1 to 9.7 resulted in the following equation:

$$R = 0.96\sqrt{1/NR} + 0.10$$

In the second stage the initial ranks (R) were realigned because the initial distribution of the R values was primarily at lower values. Ranks showing a greater degree of discrimination was desired To spread the clump of low ranks, a division was chosen at those rank. supported by data from three or more studies for the same reasons mentioned before. All the ranks could then be proportionately adjusted.

The median rank of 5.0 was set at the approximate bottom of the three study supported range. The approximate average R of the division point for all behavioral variables was R = 1.7 (range: 0.78 - 2.25). Therefore, the initial Rs of 2.0 to 10.0 were contracted to a rank dispersion of 5.0, ranging from 5.0 to 10.0, and the initial ranks of 0.1 to 2.0 were expanded to 5.0 rank dispersion, ranging

Table 4.3

A Sample Calculation* of a Reliability Rank from the Numerical Measure of Reliability (NR).

$NR = 0.2003$

$RI = 0.96\sqrt{1/NR} + 0.10 = 0.96\sqrt{1/0.2003} + 0.10 = 4.894$

$RF = 5(RI - 2)/8 + 5 = 6.808$ (use of the equation for $RI > 2.0$)

Final rank value reported as 6.8

* The sample data were for the relationship of the input variable, CAST, to the output variable, the EL ratio.

from 0.10 to 5.0. The proportional shift of R values was accomplished with the following formula to provide the final model ranks (RF):

a) for $10.0 \geq R \geq 2.0$, $RF = 5(R - 2)/8 + 5$

b) for $2.0 > R \geq 0.10$, $RF = (4.9/1.9)(R - 0.1) + 0.1$

or

$RF = 2.4758 \sqrt{1/NR} + 0.1$

An example of the entire procedure is given in Table 4.3.

By these means the rank representations of the reliability of the available data support over the range of all input variables were sufficiently spread across the range of 10 to 0. The adjustment of the ranks provided a clearer discrimination of reliability by the user. Differences between the behavioral output variables or across the range of an input variable were thereby clarified.

4.4 Diagnostic Program

After defining the reliability ranks for all input variables for each of the behavioral output variables, a diagnostic program was developed to organize and designate the appropriate ranks. The diagnostic program contains all rank values, selects the appropriate rank for the input variable(s) called by the user, calculates a composite rank for multiple input variables, and delivers a rank for each output variable and each iteration of the main model.

The diagnostic program is composed of a controlling unit, the eight subprograms generating the reliability ranks, and the manipulative subroutines (see Figure 4.3). The controlling unit is small

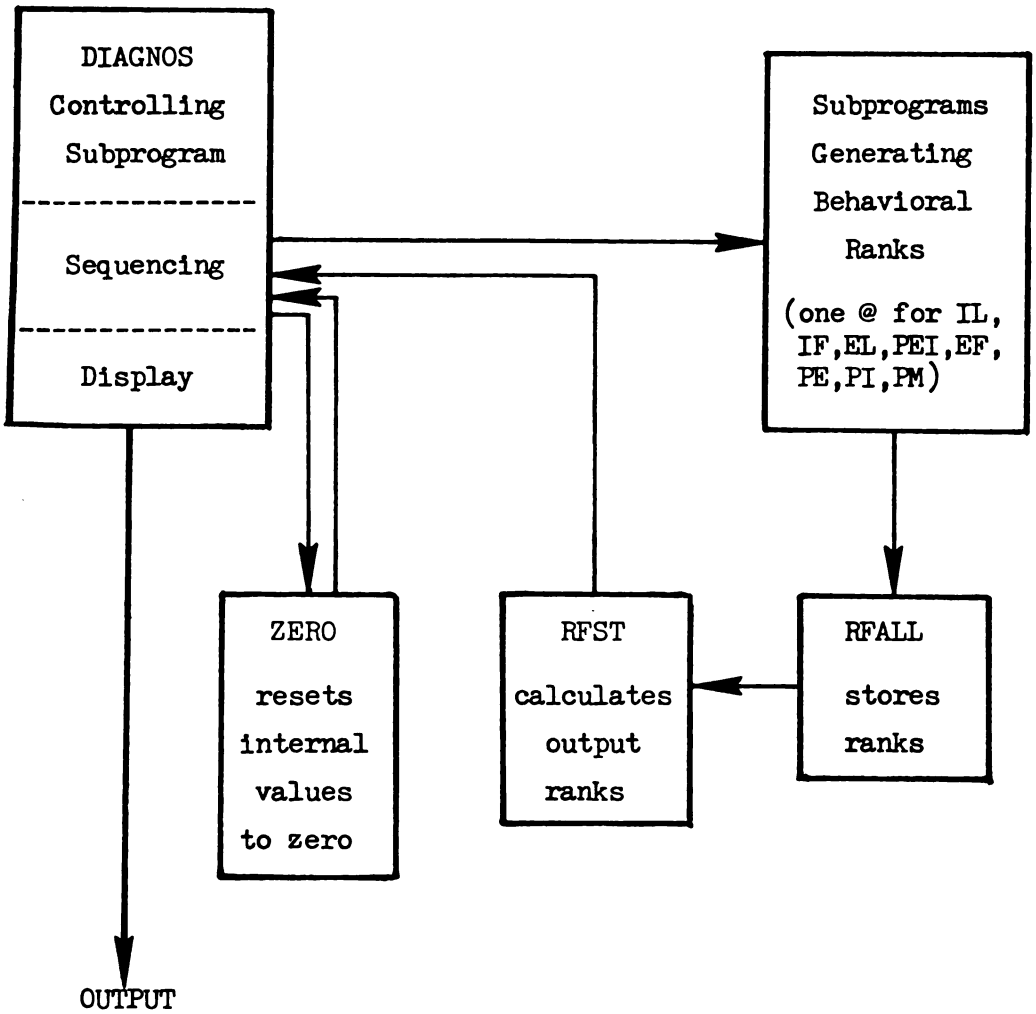

Figure 4.3 General Diagram for the Diagnostic Subprograms

and simply controls the order of implementation of the subprograms, loads the rank output matrices, and provides for a rank output display.

The eight subprograms containing the rank values for each input variable are the backbone of the diagnostic program. There is one subprogram for each behavioral output variable: IL, IF, EL, PEI, EF, PE, PI, and PM. Within each subprogram, a value other than the preset dummy value for any input variable generates a rank value. IF statements are used to test for the presence of a reset value of each input variable. In general, there is at least one IF statement for each input variable. If no data were available for a given input variable or for a part or its range, the rank setting statements for that input variable are bypassed. The omission results in the assumption of a zero rank, as the ranks are initially zero.

When a rank value is set for an input variable, it is transferred to the RFALL subroutine, that stores all ranks for each iteration of the model and for each behavioral rank subprogram. RFALL holds the reliability ranks in an array as each rank for the different designated input variables is passed from a rank subprogram. When a rank subprogram has sequenced to the end, RFALL passes the rank array to the processing subroutine, RFST.

RFST finds the minimum rank and calculates the average rank. The mean of the minimum and average rank is also calculated. The minimum-average mean is a compromise for the weaknesses inherent in both the minimum and average rank. The minimum rank too frequently is zero, which prevents discrimination among the different variable combinations and between output variables. With multiple input

variables, zero minimums were a frequent occurrence. The average rank has good discrimination, but it does not accurately reflect the reliability. In a multivariate system, the weakest element - the one with the greatest variability and least reliability - determines, in large part, the reliability of the whole. The minimum-average mean rank reflects the attributes of both, but reduces their weaknesses. The frequent minimum zero is eliminated and the average is lowered. The minimum, average, and min-av. ranks are passed through COMMON to the controlling unit for storage in the rank output arrays.

The control unit then zeros all designated ranks, using the ZERO subroutine, and calls in the next behavioral rank subprogram. This process continues through the eight subprograms, storing the ranks for each subprogram in turn. Finally, after the display of all output variables on one page, the three rank arrays are displayed by the behavioral measure and behavioral series on the following page. The entire process is repeated for each iteration of the model.

4.5 User Information

The male sexual behavior model provides information on the effects of intrinsic, stimulus, behavioral, sensory, hormone, and drug effects on the sexual behavior of the male rat. Eight behavioral measures are presented, along with two penile measures and three blood hormone concentrations. An estimate of the reliability of the output for each behavioral measure is provided in conjunction.

Input

The user can input any combination of the 112 variables incorporated in the model. A complete description of each variable and their preset values is given in Appendix A. The input variables are of three general types. The first is the simple variable, that is only one experimental condition, such as age (A) or sexual experience (SEXEXT). Almost all the simple variables are real variables, so their values exist on a continuum.

The second type is integer variables that set one of several closely related experimental treatments. The SEXSTIM variable, that can access any one of 15 different stimulus treatments - most involving the sexual object - is an example.

The third type is a variable that is associated with another variable. The associated variable can give a more specific condition of another variable, as the ISS variable sets the intensity or frequency of shock for the ISHOCK variable, that sets the general shock condition.

The remaining associated variable categories refer only to hormone treatments. An associated variable may establish a general hormone treatment condition; only a few of these exist (DPC, INJ1, and HPI), but a value for each is necessary for the calculation of the effects of the hormone treatment variables. The default values for each are all zero. Therefore, the default condition sets DPC, the time between castration and treatment, at the day of castration (a maintenance regime), INJ1 assumes one injection per day for the duration of treatment, and HPI sets sexual testing immediately after

injection.

The last associated variable category is the internally related variables. A hormone treatment condition frequently has two necessary variables, one variable establishes the hormone dosage and the other the days of treatment. For example, estradiol benzoate (EB) injection has the dosage variable, DEB, and the duration variable, EBDY. The user should check the variable list for the dose and day hormone variables and designate a value for both to be assured of intelligible results. However, not all hormone or drug conditions have both variables; in that case, the one is sufficient.

The next consideration is the incremental value required for most input variables. The model program executes a designated number of iterations, that increments each variable by the set amount of each increment value for the designated input variable, and then recalculates all output variables. When the program reads in a value for an input variable, it expects a value for the increment as well, assuming an increment variable exists for that input variable. The increments are all real elements of an array, and exist for only real input variables, that are in the majority. All increments are preset within the program, almost all to a zero value (see Appendix A).

The example in Table 4.4 shows the exact nature of a hypothetical input utilizing data cards. This example demonstrates all the basic input requirements the user need follow, although as an input list it is more complicated than most people would want. The first value (5), on the first card, is the number of desired iterations. The program will recycle five times, adding increment values for all variables each time. Each increment represents another experimental

Table 4.4

A Sample Input Variable List

Card No.	Column No. 1 7 10 15 20 30
1	5
2	A
3	300.0 7.0
4	TDN
5	13.0 -1.0
6	EICI
7	5.0 1.0
8	NEICI
9	10
10	NSEN
11	1 10
12	DPC
13	30.0 7.0
14	DTTP
15	150.0 0.0
16	DYTTP
17	7.0 7.0
18	HPI
19	5.0 0.0
20	FLAG

test of sexual behavior.

After the iteration value (NINC) come the input variables. The name of the input variable is given first (starting in column 7 of a card), and the values for that variable and its increment follow on the next card. The sequence is repeated for each variable. The final data card must be FLAG, which terminates the read-in of the variable names and values.

The number of iterations (NINC) is read according to the format (7X,I3) for integers, so the last digit rests in column 10. All the variable names start in column 7, and are followed by the variable values. The values enter under one of three formats depending on the nature of the variable.

In the example (Table 4.4), A, TDN, EICI, and the hormone variables (card 12 and below) enter according to the (10X,2F10.3) format, so the variable's real value is placed between columns 10 and 20, and the increment's real value between columns 20 and 30, in decimal form. In the case of the age variable (A), the males' age will be 300 days, and on each successive test-increment the males will be 7 days older. The TDN variable demonstrates that the increment can be negative, as well as, positive.

The EICI and NEICI are associated variables that should be designated together for the enforced interval between intromission condition. The EICI sets a 5.0 minute enforced interval for the first sexual test, and the 1.0 increment increases the interval by one minute with each successive test. The NEICI = 10 establishes that the interval is enforced between each intromission in an ejaculatory series. As the NEICI variable is integer, it has a

different format, i.e. (10X,I5), which has the last digit fall in column 15.

The NSEN array is a unique case. It has 12 elements, each a different sensory treatment. The array allows more than one sensory treatment to be designated. The NSEN array is filled according to a (6X,13I3) integer format. As the array is preloaded with neutral integers, the user need only put in the values for the desired treatment(s). The example shows two treatments requested for NSEN: the OBX (NSEN=1) and noise during testing (NSEN=10). Three columns are allowed for each integer value.

The remaining variables are hormonal and use real variable designations for the variable and its increment. Table 4.4 includes the remaining two categories of associated variable. The DPC and HPI set the general conditions for the generation of hormone responses. DPC = 30.0 designates the initial sex test at 30 days following castration, a hormonal recovery situation. HPI = 5.0 indicates the test start at 5 hours after injection for that day, and as its increment is zero; the subsequent tests occur at the same time following injection. Note that the increment for the DPC is consistent with the age (A) increment. It is preferable to keep all variables and increments consistent with one another, but not a necessity - the program will realign inconsistent values in most cases, but the realignment may not necessarily be what the user had intended.

The DTTP and DYTTP variables are internally related. Both should be designated for guaranteed results. According to the values for the variables, a dosage (DTTP) of 150 ug/day with no change on repeated test-increments is set, and the first test occurs on the

seventh day of daily injection (DYTTP = 7.0) and retesting occurs once each week, an increment of 7.0 days. This day increment, again, is consistent with the A and DPC increments.

FLAG terminates the list of variables. The program proceeds to calculate the behavioral, penile, and hormonal responses to these stated conditions.

Output

The output is in two major segments; one gives the behavioral, penile, and hormone values, and the second gives the reliability ranks for the behavior. The two segments are provided for each representation of a sexual behavior test, that occurs for each program iteration. Therefore, with an iteration value of 5, the output would consist of a single page statement of the number of increments and a list of the designated variables and their increments, followed by the six sets of the two segments, one segment to a page (see Figure 4.4).

The first segment provides values for an experimental and control male group. The behavioral measures include the IL, IF, EL, PEI, EF, PE, PI, and PM. A value is given for each measure for the control and experimental male groups for each of the five consecutive ejaculatory series designated in the model. (Alternate series numbers are obtained by changing the NSR input variable.)

In addition, ancillary behavioral values and the Experimental/Control (E/C) group ratios are supplied. The ancillary values include a calculated intercopulatory interval (ICI), that is the

MALE SEXUAL BEHAVIOR DATA

SR	IL	CIL	IF	CIF	EL	CEL	PEI	CPEI	EF	PE	CPE	PI	CPI	PM	CPM
1	47.55	47.55	11.00	11.00	442.50	442.50	323.70	319.99	6.4	.9966	.9966	.9996	.9996	1.0000	1.0000
2	0.00	0.00	5.10	5.10	235.36	235.36	412.76	372.67	6.4	.9629	.9629	.9958	.9958	1.0000	1.0000
3	0.00	0.00	5.50	5.50	270.44	270.44	493.13	445.23	6.4	.8637	.8637	.9828	.9828	1.0000	1.0000
4	0.00	0.00	5.90	5.90	274.95	274.95	587.80	530.70	6.4	.6996	.6996	.9546	.9546	1.0000	1.0000
5	0.00	0.00	6.30	6.30	349.95	349.95	693.10	625.78	6.4	.5172	.5172	.9064	.9064	.9608	.9608

ANCILLARY BEHAVIORAL VALUES

	SERIES=	1	2	3	4	5
	INTERCOPULATORY INTERVAL=	44.2499	46.1484	49.1705	46.6022	55.5470
CONTROL	INTERCOPULATORY INTERVAL=	44.2499	46.1484	49.1705	46.6022	55.5470
	TOTAL IL=	47.5299	0.0000	0.0000	0.0000	0.0000
	TOTAL IF=	9.9962	5.0784	5.4056	5.6324	5.7101
	TOTAL EL=	440.9785	226.6356	233.5842	192.3605	180.9997
	TOTAL PEI=	322.5839	397.4692	425.9303	411.2321	358.4876

CALCULATED BEHAVIORAL E/C RATIOS

SERIES=	1	2	3	4	5
EF RATIO =	1.0000	0.0000	0.0000	0.0000	0.0000
IL RATIO =	1.0000	0.0000	0.0000	0.0000	0.0000
IF RATIO =	1.0000	1.0000	1.0000	1.0000	1.0000
EL RATIO =	1.0000	1.0000	1.0000	1.0000	1.0000
PEI RATIO=	1.0116	1.1076	1.1076	1.1076	1.1076
PERCENT E RATIO =	1.0000	1.0000	1.0000	1.0000	1.0000
PERCENT I RATIO =	1.0000	1.0000	1.0000	1.0000	1.0000
PERCENT M RATIO =	1.0000	1.0000	1.0000	1.0000	1.0000

HORMONE AND PENILE DATA

TESTOSTERONE(NG/ML)	LH(NG/ML)	FSH(NG/ML)
7.296	59.777	384.592

NO. PENILE PAPILLAE = 87.300
PENIS WEIGHT = 93.000

NO. OF HORMONE MODEL CYCLES = 1

HORMONE AND PENILE E/C RATIOS

T RATIO = 2.2000
LH RATIO = 1.5600
FSH RATIO = 1.0000

PENILE PAPILLAE RATIO = 1.0000
PENIS WEIGHT RATIO = 1.0030

Figure 4.4 Sample Model Output for a Normal Control Male Rat Group.

DIAGNOSTIC RANKS

SR	IL	IF	EL	PEI	EF	PE	PI	PM
1	2.1	3.9	5.1	3.4	3.3	3.0	5.6	1.4
2	0.0	4.1	2.0	3.6	0.0	2.8	5.6	1.4
3	0.0	2.3	1.3	1.9	0.0	2.5	5.6	5.5
4	0.0	2.3	1.3	1.9	0.0	2.4	5.6	5.5
5	0.0	2.3	1.3	2.0	0.0	2.2	5.6	5.5

AVERAGE OF RANKS

1	2.9	5.0	5.2	4.4	4.9	4.1	5.6	2.8
2	0.0	5.4	3.9	4.7	0.0	4.0	5.6	2.8
3	0.0	4.6	2.7	3.9	0.0	3.6	5.6	5.5
4	0.0	4.6	2.7	3.9	0.0	3.6	5.6	5.5
5	0.0	4.6	2.7	3.9	0.0	3.3	5.6	5.5

MINIMUM RANKS

1	1.3	2.8	5.0	2.5	1.7	1.8	5.6	0.0
2	0.0	2.9	0.0	2.5	0.0	1.6	5.6	0.0
3	0.0	0.0	0.0	0.0	0.0	1.4	5.6	5.5
4	0.0	0.0	0.0	0.0	0.0	1.2	5.6	5.5
5	0.0	0.0	0.0	0.0	0.0	1.0	5.6	5.5

Figure 4.4 (cont'd)

average number of seconds required for each intromission (EL/IF), for both experimentals and controls. The other ancillary values provide the average response of the IL, IF, EL, and PEI for experimental males when the non-responding males are included in the measure average. These total male averages are generated by multiplying the appropriate male response ratios by the behavioral measure, which is the PI with the IL and the PE with the others. The E/C ratios are provided for all behavioral measures. Separate ancillary and E/C ratio values are given for each of the five ejaculatory series.

The remainder of the first segment gives the hormone and penile data. The systemic blood concentrations are provided for T, LH, and FSH for the experimental males. The number of penile papillae in cross-section and the penis weight follow. The number of hormone cycles refers to the number of times the model had to readjust the LH and FSH levels against the T levels to obtain reasonable correspondence, particularly when the plasma levels are input variables (i.e. PLT, PLLH, and PLFSH) or dosages of any of the three are input. Furthermore, the E/C ratios for all the hormonal and penile measures are included.

The second segment reports the filed reliability values for the particular combination of input variable values designated. A rank value is given for each of the eight behavioral measures in all five ejaculatory series. The reliability values are ranks from 0 to 10, and these are presented in three categories. The different categories are used to give a clearer picture of the reliability when more than one variable is utilized, as, internally, one reliability rank is designated for each input variable value. The bottom

category is the minimum rank; the middle is the average rank - the average of the ranks for each input variable. The top category is a combination of the average and minimum rank; it is an attempt to reflect the strengths of the minimum and average ranks and reduce their inherent weaknesses. Reference to the top rank category is usually sufficient for an estimate of the reliability of each behavioral measure output over the five ejaculatory series (the highest rank value is the highest reliability).

The entire sequence of information is repeated for the next iteration and each following iteration. At the last iteration, the model terminates. For another sequence of input variables, the model must be reaccessed.

Chapter 5

Effects on the Post-Ejaculatory Interval (PEI)

5.1 Introduction and Description

The post-ejaculatory interval (PEI) measure chapter provides an in depth view of the effects of all input variables with data support on the PEI. The manner these relationships are handled within the model and the decision processes involved is the sole emphasis of this break-down. The remaining male sexual behavior measures are discussed in a condensed fashion in the following chapter.

By definition, the post-ejaculatory interval is the duration (in seconds) from an ejaculation to the first intromission of the following ejaculatory series. The PEI is a behaviorally quiescent period characterized by an inactive male rat, usually reclining in a corner of the testing arena, emitting an ultrasonic series of tones, termed a "post-ejaculatory song" (6,7).

For the purpose of standardization, a normal male is considered to be at least 100 days old, sexually experienced, and tested no more frequently than once a week at approximately five hours into the rats' dark period with a sexually receptive female rat. The PEI of a normal male ranges from 100 to 800 seconds, or 1.5 to 13.5 minutes.

The normal male PEI increases in duration following each successive ejaculation. This pattern of increase pertains to a group of males; individual males are more varied in response. A composite of 55 studies published in a variety of journals provides the normal

male values for the successive PEIs. The first (PEI_1) through the fifth (PEI_5) post-ejaculatory intervals are considered.

5.2 Effect of Successive PEIs

A pattern of increasing PEI values with successive PEIs was demonstrated using data from studies reporting two or more consecutive PEIs. Multiple reported PEIs were required because the variance among studies resulted in different patterns when all studies, including those reporting only one PEI, were averaged. The mixture of studies with one or more PEI value(s) was considered less reliable, as far as the changing PEI pattern was concerned. Twenty-eight articles reported more than one successive PEI. The distribution of articles by strain was unequal. Many utilized Göteborg males (4,89,119,125, 130; N=17 experiments). Less utilized Long-Evans males (41,62,65,74; N=4), and only one study each used Charles River (170), Sherman (52), and mixed hooded and albino (30) strains.

An average value for each of five consecutive PEIs was calculated based on groups of males with five or more consecutive PEIs. This included Göteborg (119; N=6 experiments), Long-Evans (62,74), and mixed (30) strains. The following equation,

$$PEI_n = 38 \cdot SR \cdot \ln(SR) + PEI_1$$

fit the overall data nicely. The pattern was a logarithmic increase with consecutive PEIs, starting at the value given for the first PEI (PEI_1). (SR refers to the number of the PEI following the desired ejaculatory series.) This pattern held for all strains (see Figure

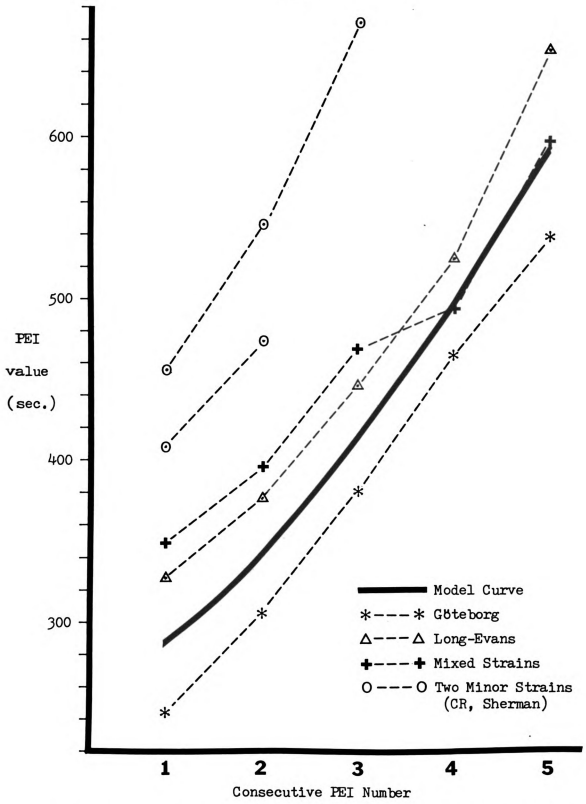

Figure 5.1 The Relation of Strain Averages to the Calculated Model Curve for Consecutive PEIs. The model PEI_1 was based on the average PEI_1 for all studies regardless of strain.

5.1). For descriptive purposes, the value of the calculated curve in Figure 5.1 was based on the average value for all strains at PEI_1. The calculated curve and those for the different strains can be seen as essentially parallel, even though the initial PEI_1 value varies. Because each strain had a different first PEI value average, the PEI_1 value was set within the model by strain. The calculation of succeeding PEIs proceeded from that value.

5.3 Strain Differences

The average PEI_1 was compared between the different available strains (Figure 5.2 & Table 5.1). The Göteborg males recovered from the PEI passivity the most rapidly, with Long-Evans and Wistar males at intermediate durations, and the slower Sprague-Dawleys had the longest PEIs. As might have been expected, the mixed strain group fell in the middle range.

The PEI response was considered different if the standard errors of the means between two strains did not overlap. Therefore, the Göteborg (G) PEI_1 value was set at 240 seconds, the Long-Evans (LE) and the Wistar (W) at 320 sec., the Sprague-Dawley (SD) at 480 sec., and the mixed strains (M) at 370 sec. These were all approximations to the nearest five seconds. The articles involved appear in Table 5.1.

The differences among strain PEIs was observed to have a genetic basis. Dewsbury (66) found by crossing four different inbred strains that the F_1 generations had shorter PEIs than the average between the two parent strains, even though the F_1 PEIs did fall between

Table 5.1

The Average Normal PEI_1 Values for Different Rat Strains.

Strain	PEI_1 ($\bar{X} \pm SE$)	N	Bibliography No.
Göteborg (G)	240.0 ± 9.1	17	119,125,130
Long-Evans (LE)	319.8 ± 11.5	7	41,62,65,74
Wistar (W)	319.3 ± 12.6	16	28,137,138,142,144, 146,179
Sprague-Dawley (SD)	482.0 ± 59.3	6	101,205
Mixed (M)	371.1 ± 22.4	7	26,30,38,52,171,179

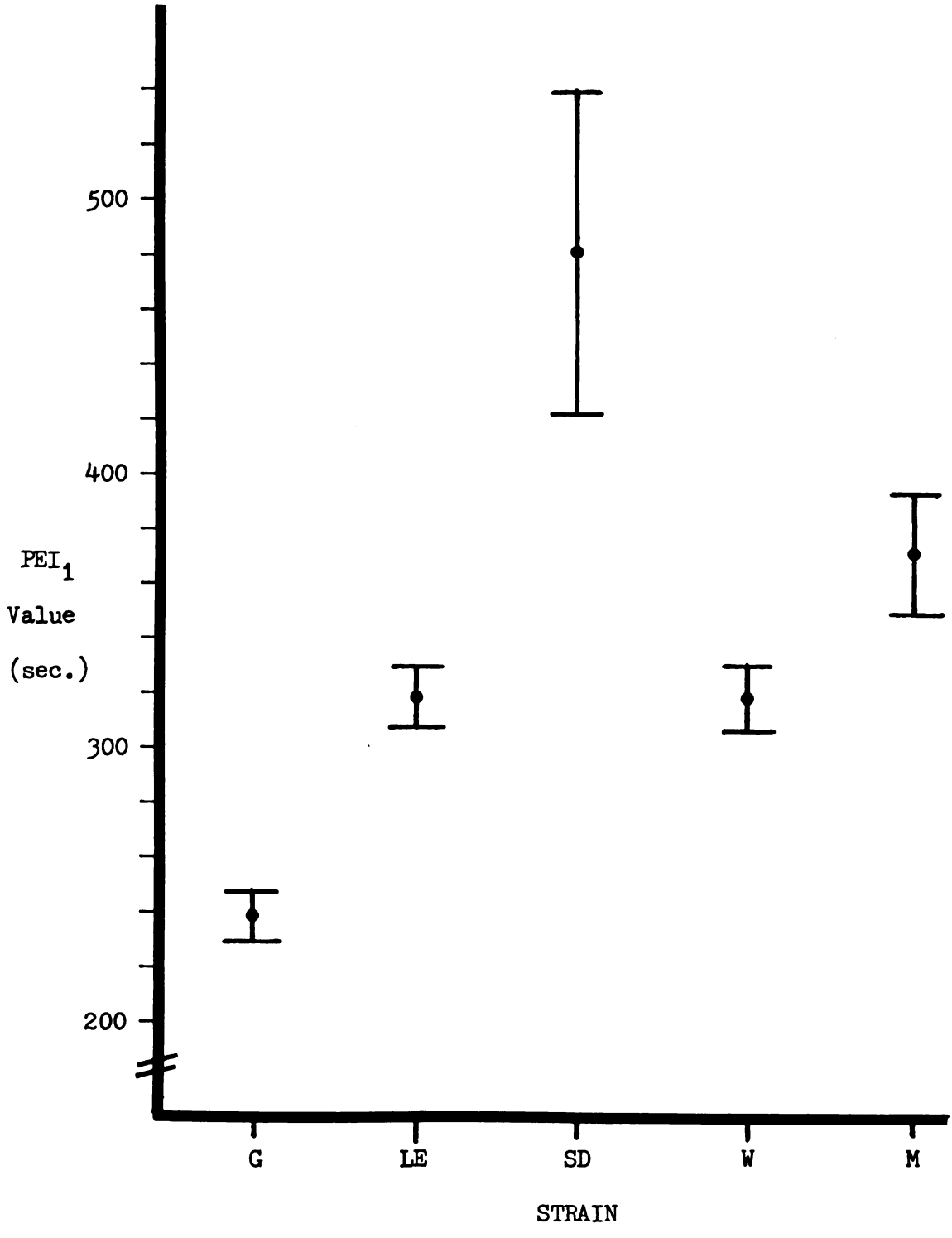

Figure 5.2 The PEI_1 Mean and Standard Error for Five Rat Strains. The actual values are given in Table 5.1 with other pertinent information.

those for the two parent strains. The lowered value would be expected on the basis of heterotic inheritance. Genetic effects were more noticeable for other behavioral measures. The indication of genetic components to the PEI gave further support to the decision to provide different PEI_1 values for different strains.

5.4 Effects of Age

The very young and the old males had longer PEIs than the normal adult males. PEI values were highest around puberty and fell rapidly to adult levels. Similarly, as males approached "senility", their PEI scores increased.

From puberty, the PEI fell exponentially (Figure 5.3) to adult levels by 150 days of age. This pattern was approximated by the equation:

$$PEI_r = ((0.12 \cdot (A-170))^2 + 225)/235 \; ; \; r \geq 1.0 \text{ at } A < 170$$

The equation provided a value for the ratio of Young/Adult male PEIs, for ages (A) less than 170 days. The exponential rise with decreasing age from 170 days was established by the square of the difference in age from 170 days. As the equation was originally derived from actual PEI values, a division by the normal PEI (235 sec.) for adults was necessary to provide a ratio applicable to any group of males.

The young age equation was derived from the average PEI values for Göteborg males. Four groups of males reported in two studies (119,140) provided data ranging from 80 to 426 days of age. The range of 158 to 426 days was assumed as the adult range as no

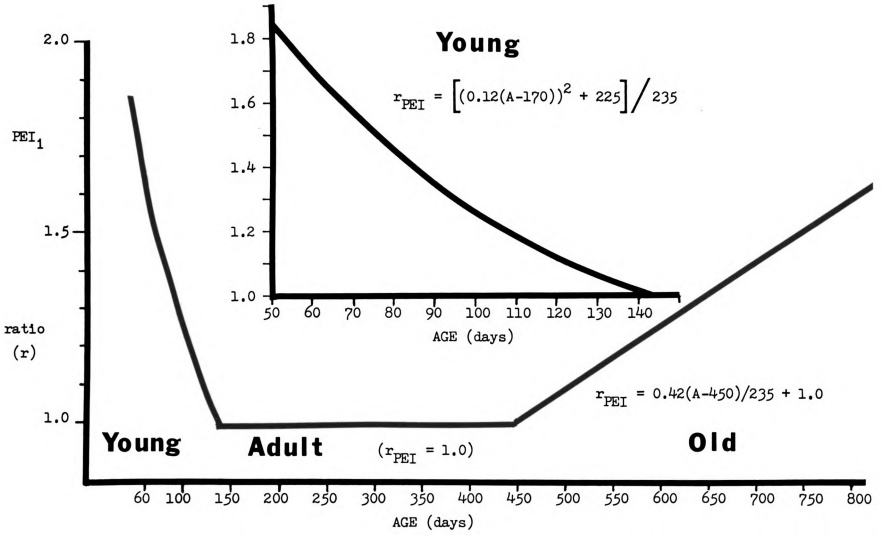

Figure 5.3 The Effect of Age on the PEI_1 Model Ratio for Male Rats. The insert expands the relationship for the young age category. The age equations are presented within the age categories.

consistent increase or decrease from the average PEI_1 value of 235 sec. was noted. Therefore, the 235 sec. value was equivalent to an r=1.0 ratio value in the equation.

Other researchers provided data on young males, but they reported only one or two data points in the young age range, and none in the adult range (170-450 days). Therefore, comparisons of young-adult age differences due to strain differences were not available. (The articles included by strain: G - 87,89,127; LE - 42,45,58,61, 62,64,65,74; SD - 205; W - 28,158,179,181; and M - 26,179,201).

The primary problem in interpreting age data was the potential interaction with sexual experience and repeated testing. The available data for age effects was based on repeated testing of the same group of males, thereby providing a series of data points of increasing age. The higher PEI_1 values at the earliest age of 80 days might, in part, be due to a lack of sexual experience. Sexual experience would have increased with repeated testing at the same time age increased. The same relation would hold for the males' familiarity with the testing environment. No experimental separation of these factors has been carried out within the published PEI data. Dewsbury (65) repeatedly tested males approximately 125 to 150 days of age and found no obvious change in PEI response. This, however, was weak evidence for a lack of experience and/or testing effect. The age range was far too narrow to show a noticeable age interaction. In addition, the age range made the comparison of the Dewsbury strain (LE) with the age equation strain (G) ineffectual.

A representation of the variation of the reported data points about the model curve was established using the mean and standard

error of the deviations of the Experimental/Control ratios from the model value. The variation with age of the young males was not consistent. Before 95 days of age, the variation (0.23 ± 0.04) was slightly larger than that for 95 to 145 days (0.16 ± 0.03). No consistent pattern of change in variation was seen over those ages. The change in variation was consistent with behavioral expectations. The PEI response was more variable at earlier ages, consistent with improving performance due to both maturation and acquired experience.

The effect of age upon the consecutive PEI increase was negligible for young males. The patterns of PEI decrease with age were parallel when consecutive PEIs were compared. PEI_2 was consistently longer than PEI_1, as PEI_3 was longer than PEI_2, and all showed the exponential increase approaching puberty. Similarly, the pattern of PEI increase due to consecutive PEIs (seen in Figure 5.1) showed the young response parallel to the adult male response. Therefore, no interaction between consecutive PEIs and early age was concluded.

A better indicator of the lack of a consecutive PEI - age interaction was the deviations from the established curves. The deviations were similar for PEI_1 through PEI_5. In fact, a slight decrease in the deviations existed with increasing PEI number for all available points (62,74,119,120,140). The variation for PEI_1 was 0.20 ± 0.03 (n=15 points), and the range of the mean deviations for PEI_2 through PEI_5 was 0.14 to 0.18 with the deviations standard error range of 0.03 to 0.04 (n=13-15 pts.). The variation was consistent about the calculated model values for all five PEIs in the range of the young ages.

The adult males aged approximately 145 to 475 days or about 5 to 16 months (Figure 5.3). As the adult age group was the normal standard of comparison for young and old ages, the relevant information has been described in the previous sections. The model ratio for the adult was 1.0, and no changes occurred in the adult age range. However, the variation with increasing PEI number was a consideration. The Göteborg strain (4,119,123,124,125,130,132) had somewhat less variation (0.16 ± 0.03, n=18 for PEI_1 to 0.11 ± 0.02, n=10 for PEI_5) than the combination of the other strains; LE (64), SD (171), & M (30); with deviations of 0.27 ± 0.11 (n=23) for PEI_1 to 0.18 ± 0.06 for PEI_5. As indicated for the young males, the same decrease in deviation occurred with the adult consecutive PEIs in all strains.

The effect of increasing old age, "senility", on PEI values was more limited than for the decreasing age pattern of the young. After 450 days of age, males showed a gradual linear increase in the PEI. The relation was represented by the equation for the line:

$$PEI_{old} = 0.42 \cdot (A - 450) + PEI_{adult} \quad ; \text{ for } A > 450$$

The equation stated that for each day beyond 450 days of age (A), 0.42 seconds were added to the PEI value for the normal adult. Unfortunately, only data for Göteborg males (119,124,132,140) was available; thus, again, strain comparisons were not possible.

The old males displayed no interaction between age and the consecutive PEIs like the young males. The consecutive PEI increase for old males was parallel to that for the adult. In addition, the pattern of PEI increase with age was parallel from PEI_1 through PEI_5.

The variation about the old age model line established a slight decrease with consecutive PEIs (Table 5.2) like the adult. The reasonable similarity in the deviations indicated the equation line adequately represented all five PEIs and not just the PEI_1 data, from which it was originally derived.

The variation across the age variable from 501 to 821 days of age (16.5 to 29 months) had no consistent pattern. The weighted average deviations of the 10 different ages in this age range was 0.122 ± 0.028 (n=3-5 pts/age).

Table 5.2

Deviations from Five Consecutive Model PEIs of Old Males.

PEI #	Deviations (X $\pm$ SE)	N_{pts}
1	0.135 ± 0.022	10
2	0.137 ± 0.022	10
3	0.119 ± 0.028	10
4	0.082 ± 0.022	5
5	0.110 ± 0.042	4

Over the entire life of the male rat, the PEI response exhibited an extended "U" shape pattern; the rapid decrease from puberty leveled out to an adult low plateau that at later ages developed a gradual increase in PEI length (Figure 5.3). In none of the three age categories was any interaction observed between age and consecutive PEIs. The variation about the model values further demonstrated the reliability of age effects across five successive

PEIs. Any relative effect of strain was left open to question, as only one strain provided sufficient data for the establishment of age patterns.

5.5 The Time of Testing

The hour of the day of sexual testing was expected to have some effect on sexual performance. The male rats' period of greatest activity was the nocturnal hours. Similarly, the rat was internally affected by daily circadian rhythms, that influenced neural functioning and blood hormone levels.

Comparisons of sexual responses during the same relative times of the dark and light periods were reported (63,119,123). Larsson tested both young (4-7 mo.) and old (14-16 mo.) males during the first four hours (123) and from the third to the eighth hours (119) of both the light and dark periods. The rats were kept on a 12 hours of light and 12 hours of dark (12L:12D) cycle. PEI values were higher during the light period than during the dark period in both studies. The PEI values were significant ($p < 0.05$) for PEI_{1-3} for the young males. As demonstrated during both the day and the night, but the effect of day testing was in the same direction in both age groups. No age interaction was indicated.

The Day/Night ratios were calculated within each experiment for comparison. The overall ratio for PEI_{1-5} was $r = 1.19$ for the younger males (123), an average of the three available ratios (1.148, 1.348, & 1.085). Curiously, the effect of day testing was significant for the normal light cycle, but when the same males were

later tested under the same regime on the reversed light cycle, no statistical effect was evident (119).

As before, no effect was seen on consecutive PEIs. The Day/Night ratios showed no consistent change over the five consecutive PEIs. Similarly, increases with consecutive PEIs were parallel when the day and the night tests were compared in the young males. No interaction was assumed between the consecutive PEIs and the time of testing.

The older males displayed an alteration of the young male responses (123). The older males had a higher average Day/Night ratio of r = 1.34 for PEI_{1-4}. However, statistical significance was found only for the third PEI. Because Larsson reported no test for interaction between testing time and age, an assumption of difference between the old and young Day/Night ratios would be unsupported. However, the ratios for both the young and old males were included in the model.

No obvious differences between young and old males were seen in the raw PEI (sec.) scores. Also, the variation about the Day/Night ratio average for each group showed no real differences (dev. = 0.086 $\pm$ 0.035 for old males and dev. = 0.094 $\pm$ 0.023 for the young) over four consecutive PEIs. The parallel increases with consecutive PEIs held for both young and old.

Although testing during the rats' daylight period prolonged the PEI response, no data demonstrating changes during the light period were reported. Only Dewsbury (63) has demonstrated a possible change during the dark period. The PEI was reported at its highest level just after the lights were turned off, and the PEI continued to decrease until near the time the lights were switched on. In two

experiments, Dewsbury (63) tested for male sexual behavior at two and four times during the dark period. The tests at different times were separated by one week and balanced according to a Latin Square design. The change over the dark period for the combined experimental data was represented by the equation:

$$PEI_1(\text{sec.}) = 240 \cdot e^{-0.23 \cdot TDN} + 240$$

The equation described a decelerating decrease in PEI_1 values from a high of 480 seconds at lights-off (TDN=0) to a low lights-on of 240 seconds (TDN=12). However, for wider applicability and use within the model, the equation was converted to a ratio equation. The above equation was divided by 320 seconds, the value approximate for both experiments at five hours after lights-off (TDN=5). Four to six hours into the dark period was the most frequently reported time of testing. Therefore, at TDN=5, the PEI ratio was set at r=1.0 with an increasing ratio at less than TDN=5 and a decreasing ratio further into the dark period. The equation became:

$$r_{PEI} = 0.75 \cdot e^{-0.23 \cdot TDN} + 0.75 \text{ ; for } TDN \leq 12$$

Although this ratio equation was known to fit only the PEI_1, it was assumed effective for the later, successive PEIs. The assumption was based on the independence of the consecutive PEI rise established in the previously discussed variables. No pattern during the light period was assumed for the model; only the overall ratio (Day/Night) over the entire period was reported.

5.6 The Time Between Tests (TBT)

The time between consecutive tests (TBT) of sexual behavior, the first of the independent testing variables, caused PEI increases when shortened (Figure 5.4). The degree of increase was less pronounced for the first PEI than for subsequent PEIs. To accommodate this finding, two equations were required:

$$r = 2.6 \cdot e^{-0.833(TBT - 0.5)} + 1.0 \quad ; \text{ for } PEI_1$$

$$r = 2.6 \cdot e^{-0.490(TBT - 0.5)} + 1.0 \quad ; \text{ for } PEI_{2-5}$$

Both equations described an accelerating increase in the PEI ratio (experimental TBT/30 day TBT) with reductions in the time between tests. The difference between PEI_1 and the remaining PEIs was one of degree rather than kind. The general shape of the equation generated curves was the same, but the exponent for the PEI_1 described an acceleration of almost twice that for PEI_{2-5}. As a result, the PEI_1 ratios became lower when the duration between tests was extended than the later PEIs.

The ratios used to generate the equations were the short TBTs divided by the long control test separations. For each particular study a period of at least two weeks (TBT=14 days) was considered a reasonable control period. The available studies had 15 (30), 30 or 60 (119) days between tests for the control. One study had a maximum TBT of 7 days (76). The ratios for this study were adjusted according to the 7 day level of the other studies. All sexual tests were extended to sexual satiety (30,76,119) or 90 minutes (30). No information was available for shorter test lengths under this

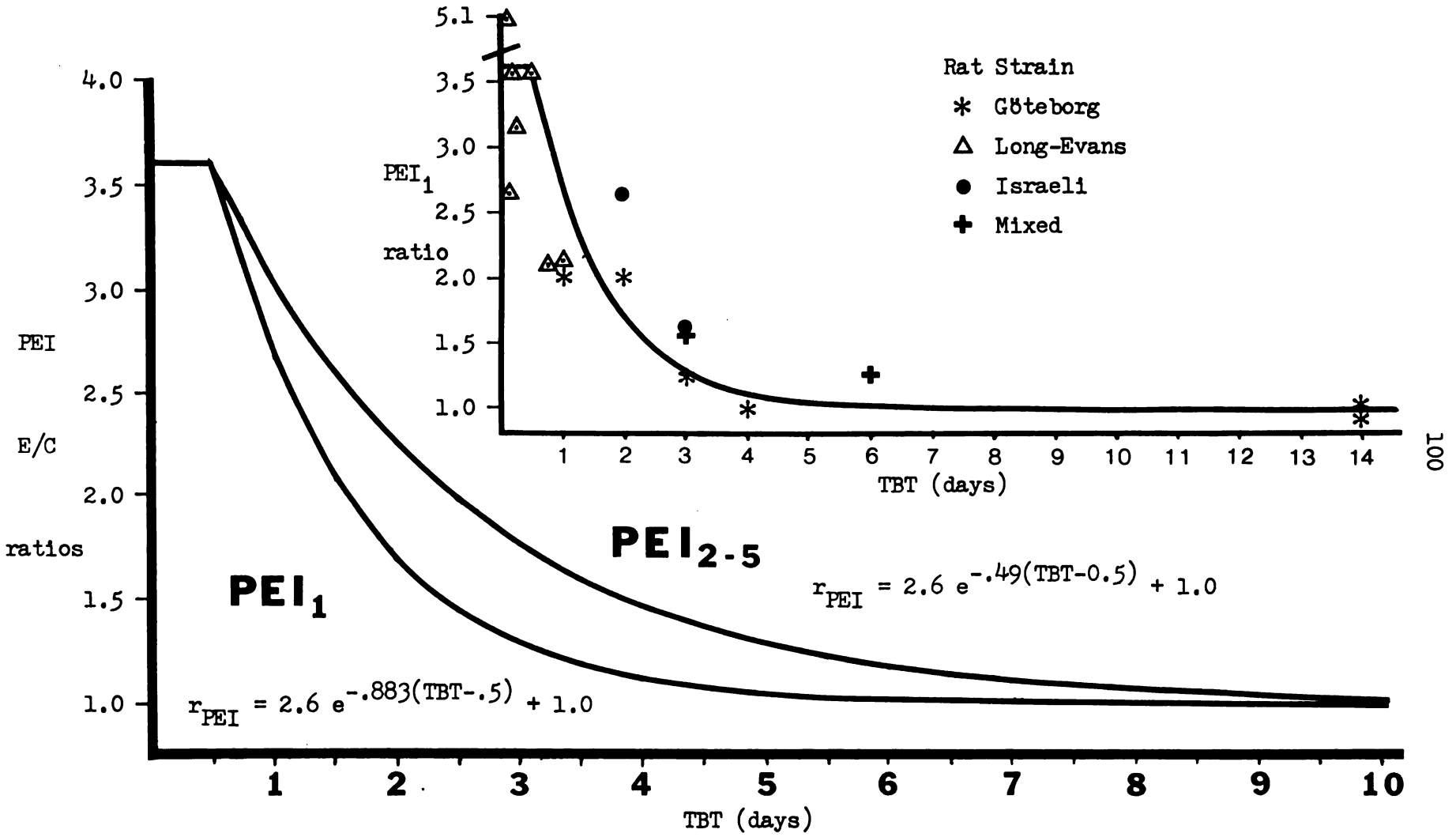

Figure 5.4 The Relation of the Time Between Tests (TBT) to the E/C Ratio in Two PEI Categories; PEI_1 and Consecutive PEIs greater than PEI_1. The inset shows the distribution of ratio points about the PEI_1 equation curve for the different strains.

experimental treatment. The remaining study provided the shortest intervals between tests (30), the various intervals within a 24 hour span between two 90 minute tests.

The ratio data points used for the PEI_1 equation fit appear in Figure 5.4. The model curve reasonably followed the distribution of points. The degree of deviation of the data was separable into two categories. The average deviation for the TBT less than or equal to one day, contained within one study (30), were 0.658 ± 0.178 ($\bar{X} \pm SE$, n=8 pts.). For TBTs greater than or equal to one day (76,119), the deviations were 0.292 ± 0.081 (n=11). The deviations about the equation values were clearly greater before one day between tests than after. However, it would be unwise to assume the difference in variation was due to strain differences (LE vs. G or M). The higher variation was more likely due to the effect of the closely timed test interval. With shorter intervals, the distinction between two separate tests and one extended test tended to fade, and as the males approached sexual satiety in an extended test, their responses became more variable.

The ratios used for the second TBT-PEI equation were based on an average PEI_{2-5}. Only data (30,76,119) for TBTs of one day or more were available. As expected, the greater variation about the second equation occurred at the shorter test intervals. The deviations were greatest at TBT=1 or 2 (0.403 ± 0.216, n=6 pts.), decreased slightly for TBT=4 and 6 days (0.327 ± 0.090, n=6), and dropped to its lowest (0.130 ± 0.018, n=11) for greater than 13 days. The degree of variation was similar to that for PEI_1.

A definite effect was found for the duration between tests of

sexual behavior. Adult males showed longer PEIs as the interval shortened, and the effect became negligible at intervals of 5 to 6 days for PEI_1 and 9 to 10 days for PEI_{2-5}. When test lengths were at least 90 minutes or to satiety, these patterns of effect held. The TBT patterns may have attenuated when test durations were shorter, i.e., testing to only the end of PEI_1, perhaps, proportional to the test length. However, no data were available using shorter test durations. This was unfortunate, because most tests of sexual behavior were less than 30 minutes in duration. Furthermore, as the interval between tests decreased, the variation in PEI response increased for all PEIs.

5.7 Sexual Experience Effects

The repeated testing of the same group of males created a confusion of sexual experience effects with those of maturation (age). Several studies (48,64,119,158,169) provided information on changing sexual experience with repeated tests. However, only one study (127) tested males of the same age with differing sexual experience. Unfortunately, no study of repeated testing effects was available, a test that would have involved testing experienced males over the same testing regime as inexperienced males at the same age.

Larsson (127) tested males with three prior sexual tests (SEXEXT=3) as males of the same age (135-138 days) with no prior experience (SEXEXT=0). With age controlled, PEIs were reported shorter for males with prior sexual experience, but the effect was not statistically significant. However, a significant decrease in

PEI occurred from the first to the second test within the inexperienced group; a similar drop occurred for the experienced group, but it was not statistically significant. Some experiential effect was indicated.

To further check for an experiential effect, studies (48,64,119, 158,169) of sexual experience of differing age were assessed. PEI both increased and decreased due to repeated testing. Admittedly, studies showing a decrease in PEI after the first test were in the majority. None of the studies reported finding statistical significance. Because of the doubt regarding the reality of sexual text experiential effects, the model assumed no effect on PEI.

This conclusion was further indicated by the experienced/inexperienced group ratios. Ratios fell both above and below the r=1.0 level. The relatively high deviations from the assumed r=1.0 suggested a cause of the statistical unreliability. The average deviations for PEI_{1-5} were 0.251 ± 0.046 (n=13 pts.).

The deviations also demonstrated a lack of any effect of consecutive PEIs. The mean deviation from the first to the fifth PEI ranged from 0.234 to 0.274, with no consistent pattern over the five PEIs.

5.8 Early Housing Effects

The housing of male rats from weaning (25-30 days of age) to adulthood had no differential effect on PEI regardless of the housing situation: isolation (one/cage), segregation (male groups), or cohabitation (mixed males and females). Three studies (87,139,206)

provided the data for the average ratios: Cohab/Seg = 0.935 (n=2), Isol/Seg = 0.990 (n=2) and Cohab/Isol = 0.887 (n=3). The individual study ratios ranged from 0.780 to 1.118. No evidence of a difference among the ratios or from the 1.0 standard ratio was indicated. The model reported no effect.

5.9 Introduction to Experimental Effects

The following experimental variables differ from the variables discussed above because they are elective experimental treatments. The above variables are intrinsic to the male rat or to the experimental testing situation. The experimental treatments include the enforcement of an interval between intromissions or enforcing an interval for the post-ejaculatory interval, changes in the stimulus value of the female sexual partner, electric shock, conditioning paradigms for approach or avoidance, and alterations of the males' environment either before or during testing. The enforced intervals are considered first.

5.10 Enforced Intromission Intervals

Creating a strict time interval between one or more intromissions (ICI) affected the subsequent PEI. The effects of enforced ICIs referred only to the PEI immediately following the manipulated ejacuatory series. No data were available for the second PEI following the manipulated series of intromissions.

The intromission interval was enforced either at one ICI or

each ICI during an ejaculatory series. The interval was enforced by removing either the female or the male from the test arena. All ratios generated for comparison were based on an ad lib. control male group, allowed no interruption of ongoing behavioral testing.

The enforcement of one ICI during an ejaculatory series occurred after the first (42,119) or the fourth (42) intromission of the first series or after the first intromission of every series extending to sexual satiety (119). The PEI decreased as the result of an enforced ICI (EICI) of from 0.25 to 7.0 minutes. The effect of removing the male from the arena did not differ from removing the female (119). The decrease in PEI was maximal for the EICIs of one minute or more.

The pattern of decrease from the ad lib. PEI to that at one minute (EICI=1.0) was not established by either study (42,119); the studies had no EICIs less than one minute. The PEI was low by EICIs of one minute and only a mild decrease occurred over longer EICIs. The data were represented by the equation:

$$r_{PEI} = 0.15 \cdot e^{-0.5 \cdot EICI} + 0.85$$

The equation described a decelerating decrease from the control level, r=1.0, at EICI=0.0 to the minimum ratio, r=0.85, by approximately EICI=7.0 (see Figure 5.5). The r_{PEI} dropped two-thirds the distance to the minimum ratio by approximately EICI=2.0 minutes.

The variation between the studies was rather high, so the variation around the calculated curve was high (dev. = 0.103 $\pm$ 0.021, n=31 pts. over PEI_{1-4}). No effect of consecutive PEIs was indicated.

The effect of the same length EICI for each intromission during

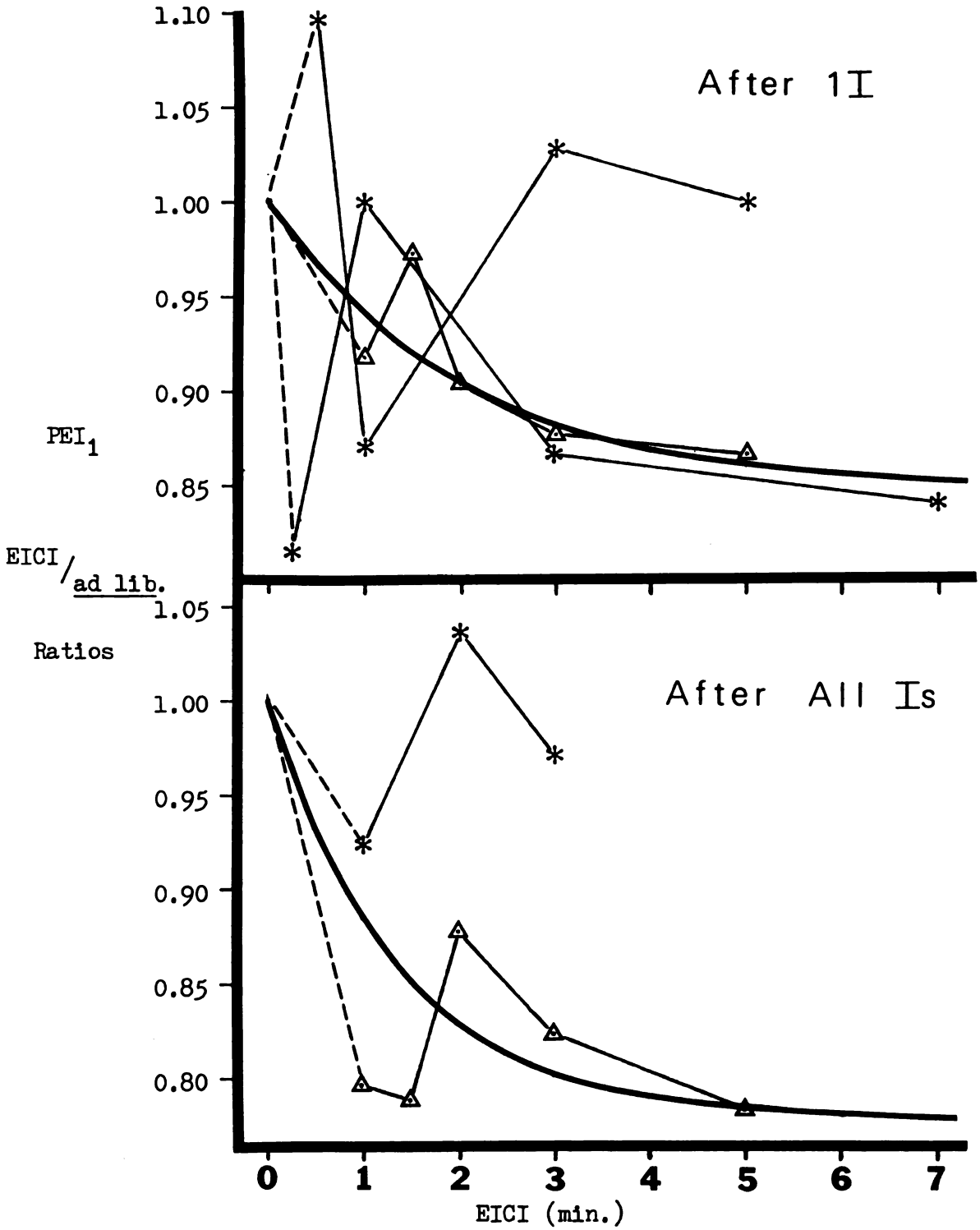

Figure 5.5 The Response of the PEI_1 Ratio to Enforced ICIs after one Intromission or after all Intromissions in an Ejaculatory Series. The reported data points appear as symbols (* Göteborg; Δ Long-Evans strains) and the model values appear as a heavy line.

an ejaculatory series was almost the same as for a single EICI in a series. Only one study (42) repeated the same treatment schedules for both enforced interval regimes, and neither study (42,119) tested for differences between the regimes. The Bermant study (42), because it used the same EICI intervals throughout a series, was given the greater weight in the equation formulation.

$$r_{PEI} = 0.22 \cdot e^{-0.75 \cdot EICI} + 0.78$$

The multiple EICI curve decelerated more rapidly than for the single EICI (0.75 vs. 0.50 for the rate exponent coefficient), and the multiple EICI treatment declined to a slightly lower minimum ratio (r_{min} = 0.78 vs. 0.85, respectively).

Because of the lack of consistency between the two studies, one (119) reporting no effect, statistically, and the other (42) a significant effect, no significant difference should be expected between the two model curves or the data supporting them. The high variation about both curves (mult. EICI dev. = 0.100 $\pm$ 0.029, n=9 ; single EICI dev. = 0.103 $\pm$ 0.021, n=31 for PEI_{1-4}) further suggested the lack of any distinction between the two treatments. Again, no indication of an interaction with consecutive PEIs was indicated.

Larsson (119) found an increased PEI when males were tested to sexual satiety (two tests to one hour on two consecutive days) three days before a multiple EICI test. The PEI ratio was r=2.0. An effect of satiety was certainly demonstrated, but an EICI effect or an interaction between EICI and satiety remained unestablished as no satiety control was reported. Regardless, the r_{PEI} = 2.0 was

incorporated in the model as an effect of the combination of EICI with satiety.

5.11 Effects of an Enforced PEI

The procedure for enforcing a predetermined interval after an ejaculation was the same as for the enforced ICI; the female partner was removed for the desired period and replaced. The measurement of the PEI response when the PEI was arbitrarily enforced appears paradoxical. However, the PEI following the enforced PEI (EPEI) was the experimental PEI measured; the following PEI was always unmanipulated. The enforced PEI was usually the first PEI occurring in the test.

The model assumed the EPEI after the first ejaculation. The EPEI ranged from 6 minutes to 72 hours, and two strains (LE (68) and G (121,122)) were involved. After 24 hours (EPEI=1440 min.), the enforced interval could be viewed as a time between tests (TBT) as easily as an EPEI. Therefore, the model will produce quizzical results if both TBT and EPEI are designated together at lengths of 24 hours or more.

The pattern of PEI response following the enforced interval was a weak downward trend to approximately 200 minutes of enforcement. The best representation for the trend was the following line:

$$r_{PEI_2} = -0.000625 \cdot EPEI + 1.05 \; ; \; EPEI < 207$$

The initial, slight increase in PEI, described by the y-intercept (1.05), was indicated by Dewsbury and Bolce (68), but they did not

carry the EPEI beyond 30 minutes; they demonstrated no significant pattern, only a potential downward trend that was highly variable. Only the Larsson study (121) provided information for EPEI values greater than 30 minutes (EPEI = 15-240 min.). The falloff in PEI length became more rapid after 24 hours (122), following the relationship:

$$r_{PEI_2} = 0.55 + 0.50\sqrt{1-(1/(-1.19\text{x}10^{-4}\cdot EPEI + 1.515))}$$

The EPEI/ad lib. ratio accelerated downward to an approximate r_{PEI} = 0.55 by 72 hours (EPEI=4320 min.), the last available data point.

The fall in PEI after 24 hours treatment was possibly a consequence of enforcing the interval after the third ejaculation (122). The drop was probably an approach to the PEI value of the first PEI of the next test. In other words, at some interval before 72 hours, responses appropriate to a time between separate tests developed. The ad lib. PEI_1 value for these Göteborg studies was about 250 seconds; PEI_4 dropped to 252 seconds after the fourth ejaculation following the enforced 72 hour $EPEI_3$. Furthermore, the PEI values for the experimental PEI_4 and PEI_5 were exactly those for an ad lib. PEI_1 and PEI_2, respectively.

The best overall statement of an enforced PEI effect was at very low EPEIs the initial, slight, nonsignificant increase in the PEI was equivalent to the slight changes induced by handling. The gradual early decreasing trend was noticeable but would not prove statistically significant without a large number of males. The longer EPEIs became equivalent to the separation between two different tests (TBT).

That the PEI following extended EPEIs approached the PEI_1 level of a second test was a reasonable assumption. Furthermore, I would expect the earlier in the behavioral sequence the EPEI occurred, the shorter the enforced interval required to attain the equivalent of a normal PEI_1.

5.12 Change of Female Stimulus

The female stimulus change involved exchanging the original female partner (same female) for a different female, having had prior sexual contact with another male (used female) or having no prior contact (fresh) that test day. The control group had the original female removed and replaced.

No effect of a female change was found for PEI_{1-5} (6,62,68, 77,101). The average different/same female PEI ratio was 1.056 (n=5 pts). The average included both fresh and used females, as no discrimination between the two was made by any study. The ratios ranged from 0.966 to 1.026.

The only actual effect of female change was to extend the duration of sexual behavior. Fisher (74) introduced a new female when the male reached sexual satiety (15 min. without a mount). The males left with the same female throughout attained an average of 8 ejaculations, but the introduction of a new female each time satiety was attained extended male performance to 12 ejaculations.

The duration of the PEIs beyond the sixth series remained about the same. The PEIs attained a plateau at an average of 824 seconds, which was approximately the PEI value for the seventh PEI.

Apparently, an upper limit existed for PEI duration.

Because the model handled only PEI_{1-5}, it treated the female change as the beginning of a new test. Therefore, the model's PEI_{1-5} actually reflected the PEI_{7-12} from the Fisher study when satiety and female change were set. The model added 518 seconds to the value of the PEI_1 for normal males and held it for five PEIs.

An alternative female stimulus was a female with the vagina sown closed (VagX), preventing intromissions. Hard and Larsson (88) allowed the males access to a VagX female for 40 minutes, while the control males were placed in a transparent cage in the test arena with a female for the same period. When both groups were tested with a normal female after the 40 minute treatment, no difference was observed between the two groups. The additional stimulation of mounting a female did not significantly alter the PEI. Intromissions and/or ejaculation were apparently necessary for the consistent increase in consecutive PEIs.

5.13 Electric Shock Stimulus

Electrical shock was delivered to males with the expectation of stimulating sexual behavior. The intensity of shock was generally set just below the squeal threshold for each male, and the shock was delivered to the males' rear; back, flank or tail; through attached wires.

Shock did reduce the length of the PEI. The average shock/no shock control ratio was $r = 0.85$ for PEI_{1-3}. No evident difference existed among the three consecutive PEIs (see Table 5.3) of six

studies (6,9,52,171,173) - one study was considered twice as two different strains (LE & SD) were used in separate experiments. The Long-Evans strain was definitely in the majority (6,9,171,173).

Table 5.3

Shock/No Shock Ratios for PEI_{1-3}

PEI #	Ratio ($\bar{X} \pm SE$)	$N_{pts.}$
1	0.859 ± 0.021	16
2	0.848 ± 0.033	6
3	0.872 ± 0.045	5

However, no evidence was found of any strain difference when the ratios were scrutinized, nor was there any difference between the LE and SD strains in the one study (171) using both strains with similar treatments.

No difference was observed for different shock rates. Caggiula and Vlahoulis (52) utilized rates of one and ten shocks per minute. Although both shock rates depressed the length of PEI_{1-2}, the depression was the same in both cases.

The addition of a bar press conditioned response to the shock treatment further decreased the PEI (173). The males were trained to press a bar to release a female into the cage for one intromission, then the shocks (1 every 30 sec.) started or the no shock-*ad lib.* condition ensued. The decrease in PEI was statistically significant under the shock plus bar press condition (Shk+BP/Shk-r=0.877), while the bar press condition alone was not significant (BP/*ad* lib.-r=0.928).

The two conditions appeared to be additive, although a minor interaction was possible.

The combined effect of the two treatments provided the BP+Shk/*ad lib.* ratio of r=0.763. The effects were almost additive because when the ratios for the treatments taken independently were multiplied,

$$\text{BP/}\underline{\text{ad lib.}} \times \text{Shk/No Shk} = 0.928 \times 0.85 = 0.789,$$

the result was not far from the effect of both (r = 0.763). The multiplication of ratios was for simplicity in modeling. The respective deviations from the 1.0 ratio were added to similar effect, (-0.072) + (-0.15) = -0.222, resulting in the additive ratio of (1 - 0.222)=0.778). The additive nature of the two treatments implied each was an independent effect.

5.14 Electroconvulsive Shock (ECS)

Beach *et al.* (26) provided information on the effect of ECS on PEIs. The shock was an electric current (65 mamps) applied across the rat's ears for 0.10 seconds, once a day for 12 days. ECS increased the duration of the PEI when the males served as their own controls (tests before and after the ECS treatment). Over 12 days of treatment, the repeated ECS treatments had a decreasing effectiveness. The ECS/pre-post treatment ratio was initially r=1.15 after 4 days of ECS and fell to about the r=1.0 level by the 12th day of treatment.

$$r_{PEI} = 0.156 \sqrt{1 - (ECSDY/12)^4} + 1.0$$

The equation described a downward acceleration of the PEI ratio.

The most rapid drop in r_{PEI} occurred at the latter days of treatment (ECSDY) with ECS, and attained the no effect level, r=1.0, at 12 days of treatment (ECSDY=12). This relationship was incorporated in the model, even though another study using ECS might have demonstrated a different relationship or no relationship.

5.15 Conditioning Effects

Male rats were conditioned to perform a task to obtain a sexual stimulus, usually a female, or to avoid elements of the sexual testing situation. Conditioning did affect latency measures such as the PEI.

Larsson (119) had tested the largest variety of conditioning paradigms, attempting to alter the rate of sexual performance. One case involved conditioning copulation to the presence of a light. During the males' training, a light was turned on, the conditioning stimulus (CS), during copulation (the unconditioned response - UCR). After each intromission or ejaculation, the light was turned off and at the start of the next intromission, it went on again, etc. During the final test session, the light was on constantly. The PEI decreased compared to an ad lib. control group. The effect, however, was not statistically significant, probably due to the low number of males (n=7) tested over three consecutive PEIs. The average E/C ratio was r=0.87.

A similar conditioning regime was the linkage of a loud bell, an aversive stimulus, to mounting the female. The treatment included removing the male from the arena for one minute (EICI=1.0) after each mount or intromission. The aversive conditioning caused a

decrement in behavioral performance; PEI scores were increased for PEI_{1-3}, but the increase was statistically significant for only the second and third PEI. The E/C average ratio for the three consecutive PEIs was r = 1.32. The ratio did not include any effect of the enforced interval; the control group experienced the one minute EICI, also.

Males were conditioned to an operant response. Males were trained to pull a pedal (CR) for access to a female (UCS) in a modified Skinner box (119). The female was removed after ejaculation and further pedal-pulls were required for her reintroduction. To assess PEI effects, the ad lib. copulation data was compared with the latency to initiate the necessary 10 pedal- pulls after ejaculation.

When the conditioned response was initiated after each ejaculation or on selected ejaculations, no consistent pattern emerged. The pedal-pull latency was significantly lower than the PEI after ejaculations 1 and 6, but was not consistently lower following ejaculations 2 through 5. These data demonstrated that male activity could be initiated prior to the end of the normal PEI duration. It did not show a direct effect on the PEI. Because of the lack of correspondence between the pedal-pull latency and the PEI, this conditioning regime was not given a PEI value in the model (i.e. r=1.0).

Other researchers have used a very similar operant conditioning paradigm for access to a receptive female. Both studies (104,173) utilized the bar press operant in a Skinner box to release the female into the box. The male was allowed one intromission before the female was removed, and bar pressing had to resume for another

intromission, etc. The PEI ratios (Cond./ad lib.) were r=1.15 (104) and r=0.927 (173); both were nonsignificant. Therefore, the no effect ratio (r=1.0) was assumed. The exception was the combined effects of bar press responses and shock reported (173) previously in the section on the effect of shock.

5.16 Group Sexual Tests

On occasion, more than one male and female were tested together in the same testing arena. Three Göteborg males (119,120) were tested with three females. The PEI_{1-5} were not different when group tested males were compared with single pair copulations. The deviations of the Group/Pair ratios from the r=1.0 were very small (0.071 $\pm$ 0.015, n=10 pts.). The model reported no change in the PEI.

5.17 Miscellaneous Stimulus Manipulations

No effect upon the PEI was observed due to exposure of the experimental male to a copulating male and female prior to the experimental sex test (90). The experimental male was placed in a transparent box with holes that was placed in the test arena where a pair of rats were copulating for a period of 40 minutes. The control males received the same treatment with no copulating pair present. The nonsignificant E/C ratio was r = 0.95 for PEI_1. The model reported no effect.

Electrical self-stimulation of the medial forebrain bundle - lateral hypothalamus resulted in nonsignificant change in the PEI

The male was trained to press a pedal (55) or lever (38) for 5 minutes (55) or to seminal emission (38). The resulting PEI ratios (E/C) were r = 1.024 (55) and r = 0.874 (38) for PEI_1. As both studies found no statistical significance and the PEI ratios existed on both sides of the null value (r=1.0), the model incorporated no PEI change.

Plastic collars, preventing genital grooming, also did not alter the PEI. Genital grooming normally would occur after every intromission and ejaculation. The experimental, long collars placed about the male's neck prevented sufficient bending to reach mouth to genitals. A control, short collar allowed the grooming. The E/C ratio was r = 1.094 for PEI_1 (96). As the effect was nonsignificant, the model reported no PEI change.

Handling the male during the course of a sexual test was often a control condition for other experimental manipulations, such as the EICI or EPEI. Larsson (132) compared the behavior of males removed from the arena approximately twice a minute and replaced with males allowed to copulate without interference. No effect of handling was found over three consecutive PEIs for young males (5-6 months old). The average Handled/ad lib. ratio was r = 0.997. However, when old males (20-24 mo.) were given the same treatment, a significant effect ($p<.05$) was found in PEI_{1-3}. The E/C ratios fell regularly from r = 0.84 on PEI_1 to r = 0.76 on PEI_3. The change over consecutive PEIs conformed to the line:

$$r_{PEI} = -0.04 \cdot SR + 0.88 \quad (SR \text{ is the PEI number})$$

Handling retarded the increasing PEI length that occurred with

increasing old age, creating a definite age - handling interaction. In addition, the inhibition of the age induced PEI rise increased with progressive PEIs. The inhibition of the age PEI by handling resulted in an actual approach of the PEI length to that of the adult male.

5.18 Introduction to Sensory Organ Manipulations

The surgical removal of a sense organ or the sectioning of an appropriate sensory nerve was the usual manipulation of a range of sensory stimuli present in the sexual test environment. The reported procedures included the removal of smell by excision of the olfactory bulbs or the chemical destruction of the olfactory mucosa, the removal of sight by blinding via enucleation, and the elimination of somatosensory information by cutting nerves to the penis and penile anesthesia. Why no study of hearing was attempted remains a mystery.

5.19 Olfactory Bulbectomy (OBX) and Peripheral Anosmia

The bilateral removal of the olfactory bulbs was the primary procedure for the elimination of smell. In a few cases, associated brain areas were removed, such as the olfactory tubercle (100) or the olfactory peduncle (138). No obvious difference was seen among these alternative treatments. The surgical operation occurred when the males were 6 to 240 days of age, but the average treatment age was about 120 days.

All articles reported some measure of the effectiveness of their technique. Some (137,138,139,168,206) made use of an odor

preference test, where the male had to locate a randomly placed, hidden food source. Other researchers made a histological check of the extent of damage to neural tissue (45,100) or a less rigorous, gross examination of the whole brain (98,139).

A variety of rat strains were represented, and the majority of male groups were sexually experienced prior to OBX (45,98,100,137, 138). However, three studies were assumed to use inexperienced males as the olfactory bulbs were removed at 6 (168), 30 (183), or 80 (139) days of age.

An average OBX/control (sham or intact) was generated based on ratios from each study and experiment within a study. The average OBX/C ratio of one ratio per study was r = 1.253 (n=8 pts.). The average ratio for all experiments was r = 1.248 (n=16). The model incorporated a PEI ratio of $r_{PEI} = 1.25$.

The statistical significance of the OBX treatment for PEIs directly determined the reliability of the assumed model ratio. Unfortunately, only three Larsson studies (98,138,183), utilizing different strains, reported statistically significant effects. The significant ratios ranged from 1.23 to 1.86. Furthermore, only one of the nonsignificant studies (168) could be seriously faulted for the surgical technique, in addition to an overly low number of males (n=3) with successful lesions.

Although the majority of studies (45,100,137,139,168) found no statistical significance due to OBX, all the PEI ratios were above r = 1.0. The range of these ratios was 1.02 to 1.28. However, the finding in 8 studies that all OBX groups were above their controls was statistically significant ($p<.004$ - Wilcoxon's signed-ranks

test). Therefore, the average ratio was considered reliable; there was a real effect of OBX on PEI.

The data for peripheral anosmia, the chemical destruction of the nasal mucosa, demonstrated no obvious difference from OBX treatments (138). The E/C ratios for olfactory peduncle oblation ($r = 1.226$) and peripheral anosmia ($r = 1.373$) were both statistically significant ($p<.005$). As no statistical test was made between the OBX and anosmic groups (they were separate experiments), and the ratios were close, no difference between the two treatments was assumed.

No consistent pattern emerged regarding prior sexual experience or the age of treatment. Both significant and nonsignificant effects were reported for experienced and inexperienced males. As the inexperienced males were treated earlier (A = 6-80 days) in life than the experienced males (A = 125-240 days), the same conclusion must hold for the age of treatment.

5.20 The Effect of Blinding

The removal of sight by enucleation resulted in a reduced PEI. The depression of the PEI was significant ($p<.05$) for PEI_1 (89). The PEI_2 had a larger difference between blind and intact males, but the difference was not significant for experienced males. The Blind/Intact ratios were $r_{PEI_1} = 0.897$ and $r_{PEI_2} = 0.873$. As the ratios were very close, their average ($r=0.885$) was incorporated in the model for all PEIs.

5.21 The Effects of Penile Nerve Cuts (PNX)

Severing and often sectioning one of the set of nerves innervating the penis and/or the pelvic region was one procedure for reducing or eliminating sensory information from the penile region. Larsson and Södersten (142) removed a 5 mm bilateral section from the dorsal penile nerve close to the pubic symphysis. A significant increase in the PEI_1 was observed, although the change in actual PEI values was small. The Cut/Sham median ratio was r = 1.069.

When the nerve cut and sham males were further treated to penile desensitization by the application of a topical anesthetic (Lidocaine), both male groups ceased ejaculation (142). Therefore, no PEI values were available, so the ratio, r = 0.0, must be assumed for penile anesthesia. The anesthesia obviously removed penile sensory information that the dorsal penile nerve cut did not.

Vomachka (198) also severed the dorsal penile nerve, but unlike the previous study, he castrated all males and provided immediate hormone replacement (500 ug TP/rat/day). The nerve cut after hormone replacement reduced the number of males attaining ejaculation. Therefore, the changes in the PEI were based on only a few males.

The average Cut/Sham PEI_1 ratio over three repeated tests was r = 1.093 (n=6 pts.), and the average for PEI_2 was r = 0.998 (n=3). Neither of the differences were significant.

A similar result was found in a second experiment (198) under three different hormone treatments. A cut and a sham group were treated with testosterone propionate (500 ug TP/day), fluoxymesterone (500 ug FM/day), or the oil vehicle. Fewer males attained at

least one ejaculation than in the prior experiment, so the calculated ratios were less reliable (PNX groups generally had only 1 to 2 males attaining ejaculation). None of the PNX groups significantly differed from the shams. The average Cut/Sham ratio over 12 repeated tests at 4 day intervals for the three hormone groups were: r_{TP} = 1.070 (n=12), r_{FM} = 1.100 (n=4), and r_{Oil} = 1.001 (n=2) for PEI_1. No data were available for PEI_2 as PNX males never completed a second ejaculation.

The ratios available for the calculation of a composite ratio, therefore, were r = 1.069 (142) and r = 1.093 plus r = 1.070, 1.100, & 1.001 (198). The average ratio, whether all were used or one ratio per experiment was used, became r = 1.07 for PEI_1. As only one experiment reported a ratio (142) for PEI_2 of r = 0.998, the r = 1.0 was incorporated by the model. The elimination of PEI due to the elimination of ejaculation was handled by the model values for the PEPIPM section. The PNX/Sham ratio of r = 1.07 was incorporated into the model, not because of statistical significance, but because every ratio was above 1.0.

5.22 Hormone Variable Introduction

Each hormone treatment potentially has a time and a dosage variable. Castrated male rats are usually injected with a particular hormone or drug dosage once a day over a period of days. Changes in the behavioral measures develop over a number of days, dependent on the hormone dosage.

An alternative to injection delivery, infrequently utilized, is

the subcutaneous implantation of a silastic capsule containing crystalline or concentrated hormone. The implant releases hormone continuously over several days, while a daily injection is a periodic pulse. However, the implant dosage is difficult to determine. As the release of hormone from the silastic tube is a function of the surface area, the length of similar diameter tubing serves a relative measure of the dosage.

Two alternative hormonal regimes are utilized. The maintenance regime initiates hormone treatments immediately after castration. The recovery regime begins hormonal treatments after the males' behavioral response has dropped to a near zero level (i.e., no intromission) well after castration. Frequently, the cessation of sexual behavior is assumed and hormone treatments are started at least two weeks after castration. The recovery of sexual activity is then observed with repeated testing under continuous hormone treatment. The different regimes are discriminated within the model by the DPC variable, the number of days between castration and the start of any treatment. The maintenance regime requires a DPC between 0 and 4 days and the recovery regime requires a DPC greater than 14 days.

Hormonal treatments are categorized into five groups. The common gonadal hormone treatments are the first division. The treatments include castration, injection or implantation of various forms of testosterone, various estrogens, or both. The second division includes the injection of 13 different androgens, but not testosterone. A number of surgical treatments of the endocrine glands comprise the third; hypophysectomy, adrenalectomy,

throidectomy, and pinealectomy are alternatives. The fourth contains nongonadal hormones: LH, FSH, prolactin, HCG, or two forms of progesterone or pregnenolone. The final division deals with the injection of various anti-androgens, anti-estrogens, androgen mimetics, or aromatase enzyme inhibitor drugs. All but the mimetic are usually combined with a gonadal hormone, most frequently, testosterone. The division containing the most data is the gonadal hormone treatment group.

5.23 Gonadal Hormone Treatment Effects

The Effect of Castration

Castration resulted in a continual increase in the PEI over the days following castration until ejaculation ceased and the PEI was eliminated. The postcastration PEI was derived from the adjusted means of five studies using Long-Evans (58,59,198) and Sprague-Dawley (106,205) males. Testing occurred twice/week (59), once/week (58,160,198), or once every two weeks (205). The maximum number of days with reported PEIs was 70 days, and only two studies (58,205) reported for more than 35 days postcastration. The response change after the cessation of testosterone (500 ug TP/day) maintenance (198) was used as a treatment analogous to castration.

The PEI followed an accelerating pattern (Figure 5.6) until males failed to complete a PEI. The change in PEI was approximated by the equation:

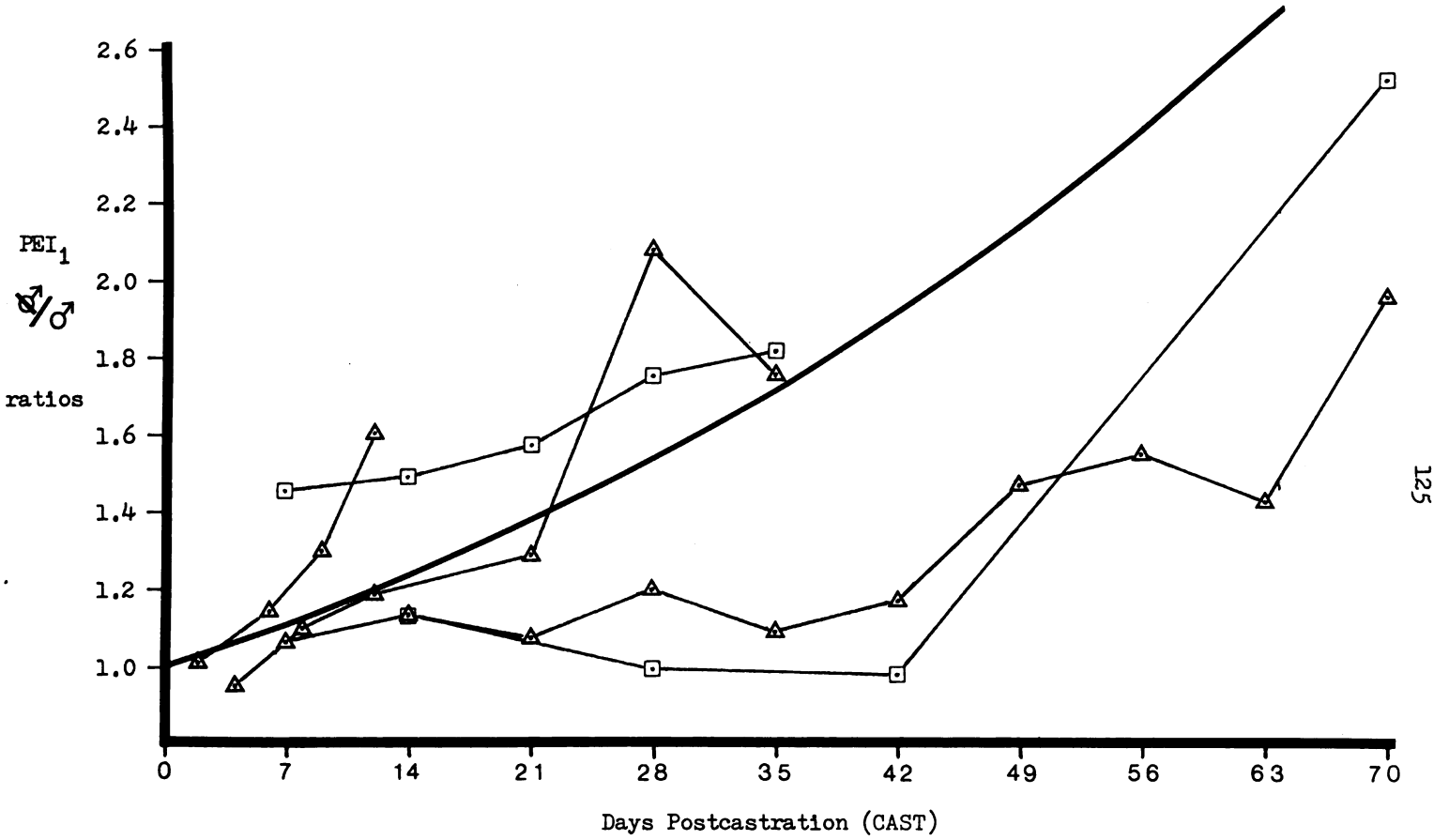

Figure 5.6 Comparison of the Model Generated Curve with the Individual PEI_1 Castrate/Intact Ratios from Available Studies. Data from a single study are connected with lines (Δ Long-Evans; □ Sprague-Dawley) and the model values appear as a heavy line.

$$r_{PEI} = e^{-0.0156 \cdot CAST}$$

The function, e^{-x}, equalled 1.0 at x=0 and rose thereafter. The castrate/intact ratio (r_{PEI}) accelerated from r = 1.0 to r = 2.98 by 70 days postcastration (CAST=70).

The fluctuations in PEI response also increased postcastration, which was demonstrated by the variation about the calculated equation curve. The measures ($\bar{X}$ & SE) of the deviations of data ratios were separable into two groups, those for 35 days or less postcastration and those after 35 days postcastration. Within each division, the means and standard errors overlapped. The deviations were 0.227 $\pm$ 0.088 averaged over CAST of 2 to 35 days (n=35 pts., n=5 av. pts.) and 0.831 $\pm$ 0.177 for greater than CAST=35 (n=7 pts., n=3 av. pts.). The deviations noticeably increased after 35 days postcastration. Apparently, as the PEI response began to disappear, the measure varied more and more. The number of males responding (see PE section) decreased, adding to the statistical variability. This behavioral decay was further substantiated by the consistent increase in the standard errors of the deviations for 42 days postcastration onward. The SE rose from 0.090 at CAST=42 to 0.169 at CAST=56 and finally to 0.276 at CAST=70.

The model equation approximated the PEI_2 ratios as well. PEI_2 increased from 4 to 12 days postcastration (198). By 21 days postcastration, no PEI_1 occurred. The deviations from the model curve were 0.030 $\pm$ 0.012 (n=3), indicating a good fit.

The effects on the third PEI were more doubtful. Vomachka (198) reported no response, but Davidson (58) did report PEI_3 values from

7 to 21 days after castration. The PEI_3 castrate ratios all fluctuated around r=1.0 with deviations of 0.127 $\pm$ 0.032 from r = 1.0. The model, therefore, incorporated the no effect ratio (1.0) for PEI_{3-5}.

Testosterone Treatments

The data for the effects of testosterone dosages of either free testosterone (T) or testosterone propionate (TP) on PEI were limited. Four studies (28,57,157,177) reported multiple dosages of T or TP, but only two (28,57) utilized dosages less than an equivalent of 50 ug/day.

Beach and Holtz-Tucker (28) utilized four doses of TP ranging from 25 to 500 ug/day. The castrate males were injected on a maintenance regime. PEIs attained the equivalent of intact male PEIs by 100 ug/day dosage. The TP/normal PEI ratios dropped to approximately 1.0 by 100 ug and significantly ($p<.02$) increased with decreasing dosage. The 25 and 50 ug/day dosages provided values for the line equation:

$$r_{PEI} = -0.0033 \cdot DTTP + 1.313 \text{ ; when } r_{PEI} \geq 1.0$$

The line terminated at the 1.0 ratio at approximately a 95 ug dosage, and rose linearly to the ratio of 1.313 at DTTP=0. However, the model will respond with ratios for the castration variable rather than the testosterone variable (DTTP) for the oil injected control (DTTP=0).

A similar PEI response with testosterone was found by Damassa et al. (57). In this case, testosterone was administered via silastic

implants of differing length under the maintenance regime. A rise in the PEI was seen with decreasing dosage (mm of implanted tubing). Several data points were available for tubing lengths of 2 to 60 mm. The PEI implant/intact ratios indicated a curvilinear change over varying dosage.

$$r_{PEI} = 0.375 \cdot e^{-0.198 \cdot TIMP} + 1.0$$

The equation described an increase in the PEI ratio from about 30 mm implant length (TIMP=30 mm) to a maximum ratio of 1.375 at TIMP = 0. The increase over T dosage was significant ($p<.01$), and the implant length was linearly related to plasma T levels (see Testosterone section)*.

When the Beach and Holtz-Tucker study ratios were fitted to the equation for the Damassa et al. study, the different dosage systems could be compared. The resulting equation was:

$$r_{PEI} = 0.375 \cdot e^{-0.0191 \cdot DTTP} + 1.0$$

Comparison of the two dosage systems gave the equivalence of a 1.0 mm T implant to the injection of approximately 10 ug/day of TP, established from the coefficients of the two equations (mm T/ug TP - 0.198/0.0191 = 10.37).

The two remaining studies (157,177), utilizing a recovery regime added no further information. All the ratios did not deviate noticeably from r = 1.0. The ratios for 1 and 3 mg T (157) and for

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* 1 mm in implant length was equivalent to an increase of 0.052 ng/ml of plasma T (57).

50 to 1000 ug TP (177) ranged from 0.956 to 1.096.

No indication of differences due to the two injection regimes was noticed after several days of treatment. Although different strains were used, no effect due to strain could be ascertained.

Other testosterone treatment data were reported, but they added little to the picture. Five papers (159,160,161,198,205) reported repeated tests with injection of a single dosage of testosterone utilizing a maintenance regime. No data for PEI were available under recovery regime.

With the maintenance regime, no consistent deviation from the null ratio (r=1.0) was observed. The days of testing ranged from 4 to 70 days with daily injection of T (205) or TP (159,160,161,198) for three different strains. The single dosage ranged from 75 to 800 ug/day, and testing occurred at intervals of 4 to 14 days. Therefore, under maintenance (DPC = 0-4) for 75 ug T or TP or more, no change from the intact male PEI was assumed.

As no evidence of an interaction between days of treatment and dosage had been shown, the model assumed none. Therefore, for low doses of T or TP, the model provided the same elevation in PEI over all days of treatment based on the dosage equations.

The PEI_1 was very stable over days of treatment. No consistent changes in the deviations from r=1.0 were observed over repeated testing. The deviations were segregated into segments of 4-8, 12-17, 19-23, etc. of weekly test groups. The deviation means varied from 0.072 to 0.028, showing no pattern of change over the range of daily treatment.

The effects of TP on PEI_2 over days of treatment under the

maintenance regime closely followed that of the PEI_1. The TP/intact ratios fluctuated about the r = 1.0, null ratio over 4 to 57 days of treatment with 500 ug TP (Vomachka, per. com.). The deviations (0.072 $\pm$ 0.017 (n=16)) were equivalent to those shown for PEI_1. Because the effects were parallel for PEI_1 and PEI_2, the model generations for PEI were assumed to hold for all consecutive PEIs in testosterone treated castrate males.

The Effect of Age of Castration on Response to TP

Larsson (133) indicated a trend toward increased PEI with early age of castration. Castration at 7 days of age produced PEI responses somewhat higher than for males castrated at 10, 13, or 19 days of age, but the change was nonsignificant. PEIs were measured at 90 to 100 days of age following treatment with 125 ug/kg BW (kg of body weight) of TP (approximately 30-35 ug/rat/day).

The primary problem with early castration was the reduction in the number of males attaining at least one ejaculation as adults; the earlier the castration, the fewer males that responded. The reduced male number might have produced artifactual changes in the PEI. The extreme case was the group of males castrated at 4 days of age that produced an insufficient number of males with ejaculation to generate a reliable mean.

If the increasing PEI trend were real, it would fit the equation:

$$r_{PEI} = -0.15 \cdot CASTD + 2.50 \text{ ; for } r > 1.0$$

The equation line was fitted to two points, the Day 7 castration

ratio (r=1.444) and Day 10 (r = 1.0 at approx. CASTD = 10.) castration. Although the effect on the PEI has not been definitely substantiated, the increase in PEI parallelled the decay of the PEI response shown by low testosterone dosages after adult castration. As some debilitation due to early castration was reasonable, the equation was included in the model.

Estrogen Treatments

The PEI response to estrogen was minimal and often inconclusive. The only available studies reporting PEI values utilized a benzoate (EB) or diproprionate (EdP) form of estradiol. Treatment under both maintenance and recovery regimes was available. The control groups were intact males, testosterone injected castrate males, or precastration tests for the experimental males.

Effects under the recovery regime proved to be the more elusive. Five articles (11,164,176,177,181) reported PEI data for 1 to 100 ug of EB injected for a period of 19 to 60 days, starting 31 to 70 days postcastration. The control males received 100 to 200 ug TP or 1000 ug T over the same treatment periods. No consistent relationship of dosage, strain, or period of treatment was observed. The EB/TTP ratios ranged from 1.079 to 1.291 (1 pt./experiment) for, presumably, PEI_1 (some studies did not specify the number of the PEI or the test length).

The overall recovery ratio was r = 1.16. The ratio was considered reliable because all six points comprising the average were greater than 1.0. The deviations about the average ratio,

0.052 $\pm$ 0.016 (n=6), were small. No indication was given of any effect occurring due to the length of treatment. Some effect on the PEI would be reasonable during the early stages of EB treatment, but data were not reported in that range. Bear in mind, the PEI values were from only responding males and frequently, many males did not attain the first ejaculation under EB treatment (see PE section).

Only one study (176) reported more than one dosage of EB. Three dosages; 5, 50, and 200 ug/kg BW (approximately 2 - 80 ug/rat/day); were given for three weeks to intact males. No consistent dose response was evident. The mild elevation of PEI due to EB injection was within range of that of the castrate males similarly treated (r = 1.21 to 1.36). Because of the similarity in response between castrate and intact males, both were included in the overall model ratio (r = 1.16).

The maintenance regime data was more explicable. Males were injected with 70 (59) or 150 (82) ug/day EB and 150 ug/day EdP (160) for 12 to 49 days, starting at castration. No consistent change from the intact (59,160) or 150 ug TP controls (82) occurred. Over the days of treatment, the PEI ratios fluctuated around the null ratio (r=1.0). The deviations from the null ratio were small (dev. = 0.073 $\pm$ 0.017, n=14). No effect on the PEI was assumed.

Estradiol in either of its longer lasting forms had little or no effect on PEI in castrate and intact males. No change occurred under a maintenance regime, but some increase in PEI was seen under recovery. The recovery increase was statistically nonsignificant in the individual studies, but it was consistent over all studies. Any noticeable change in PEI due to estrogen treatment might have been

prevented by the frequent lack of ejaculation.

5.24 Androgen Effects

Information was available on a variety of androgens utilizing both maintenance and recovery regimes. The effectiveness of an androgen induced PEI response was demonstrated by comparison with the PEI induced by the testosterone (T or TP) control in castrate rats. The minor androgens included: dihydrotestosterone (DHT), androstenediol (Aeol), androstenedione (Aeone), 19-hydroxyandrostenedione (HAeone), 3α- and 3β-androstanediol (Aaol), androstanedione (Aaone), and 19-hydroxytestosterone (HTP). Combinations of EB and testosterone with DHT and other androgens has been reported, also.

Dihydrotestosterone (DHT)

Dihydrotestosterone has been utilized in both its free (DHT) and propionate (DHTP) forms under both maintenance and recovery regimes. The PEI data using a recovery regime was, however, more scanty.

Three studies (12,164,177) reported data using recovery conditions. However, the reported PEI values were averages for the entire experiments, so changes over repeated days of DHT treatment could not be established. Free DHT was injected in 0.5 (177) and 1.0 (164) mg dosages, and DHTP was injected in a 200 ug dosage. The castrate males were injected for 26 to 36 days after a wait of 42 or 70 days after castration. All males were sexually experienced.

The DHT(P)/TP recovery ratios fell both above and below the

r = 1.0 value, and at least one ratio was statistically significant in either direction. The bidirectionality of the PEI effect presented a difficulty because the model required a single effect ratio; there was no basis for differentiating a significant rise from a significant fall in PEI based on the DHT(P) treatment procedures. No consistent differences existed for sexual experience, duration of injection, time postcastration, or the number of the PEI (all were for PEI_1). The only experimental difference was found for the time between sex tests. The two high ratios (r = 2.034 (12) & 2.075 (177)) were tested at two (12) and three (177) day intervals, while the low ratio (r = 0.693) had weekly treatment (TBT=7) intervals (164). However, as the males were tested to only the end of PEI_1, a test interval (TBT) effect was questionable. Remember, the effects on PEI due to TBT occurred for tests to sexual satiety. The bipolar effect may well have been due to some property of the PEI, as yet unknown, or simply an experimental artifact - although a significant one.

As the cause of the bipolar DHT(P) effect were in contest and the other model values were averaged ratios, the DHT(P) ratios were also averaged. The resulting average was r = 1.60. Consequently, the deviations (0.586 ± 0.191, n=3) from the calculated ratio were large.

Unlike the recovery data, maintenance data presented a range of points over the treatment period. Five studies (159,160,161,163,205) provided data on sexually experienced males over days of treatment. Four of the studies (159,160,161,163) emerged from Parrott's laboratory, so internal consistency existed for much of the data.

The Parrott data provided no evidence of differences from 75 to 200 ug of DHT(P). Similarly, no differences due to strain (Wistar (159, 161,163) vs. Sprague-Dawley (160)) were observed. The study average ratios ranged from 1.607 to 1.747. The remaining study (205) utilized Sprague-Dawleys injected with 800 ug DHT, and its average ratio was r = 1.590, sufficiently close to the other ratios to be equivalent.

No consistent changes in the PEI were seen over the treatment periods of 21 to 70 days of injection for tests given at weekly (159, 160,161,163) intervals or every two weeks (205). The average of all studies, r = 1.66, was assumed for all DHT(P) maintenance treatments.

The lack of change over days of injection was demonstrated by the deviations from the model ratio of 1.66. The means and standard errors of the deviations were generated for each week of treatment, producing six deviation groupings. The range of means was 0.148 to 0.337 and the standard errors ranged from 0.029 to 0.168. Neither the high nor the low endpoint of the ranges fell at the beginning or end of testing. Although no change was seen after 7 days of treatment, nothing was reported regarding the first few days of treatment.

The PEI average ratios attained under both the recovery and the maintenance regimes were essentially equivalent, r = 1.60 under recovery and r = 1.66 under maintenance. As far more data were available to support the maintenance ratio, 1.66 was the assumed ratio for the model for both regimes. The PEI ratio response to DHT(P) was assumed for both sexually experienced and inexperienced males.

The Combination of Estrogen with DHT(P)

Effective dosages of EB and DHT(P) produced results equivalent to TP treated males. The production of a normal PEI response occurred under both recovery and maintenance regimes. The injection of 2 ug EB with 200 ug DHTP at 31 days postcastration (11) produced the same PEIs as 200 ug TP. Larsson, Södersten, and Beyer (144) demonstrated a dose response for 0.05 to 50 ug EB given in conjunction with 1.0 mg of DHT at 50 days postcastration. The PEI approximated that of the intact male with the 0.5 ug EB or more combinations. At lower dosages, the response followed a linear relation:

$$r_{PEI} = -DEB + 1.57$$

Larsson *et al.* (145) combined 500 ug DHT with 1 and 5 ug of free estradiol (E_2) or estrone (E_1). No PEI differences were found between the two estrogens with DHT or between the two estrogen dosages. However, TP control values were not presented. No differences from TP castrate or intact males was assumed, because the E_1 or E_2 + DHT PEI values were within the range of PEI controls reported in other Larsson studies using the same strain (144,177,181) one year prior. The same lack of effect was observed with 100 ug of EdP and 100 ug DHTP when treatment began at castration (163).

Therefore, the combination of estrogen with DHT(P) in castrate males did not affect the intact PEI level response until the dosage of estrogen fell below 0.5 ug. This held for both the recovery and maintenance regimes.

Combination of Testosterone with DHT(P)

The addition of testosterone washed out any effect of DHT(P) on the PEI. After 25 or more days treatment postcastration, 200 ug DHTP with 4 ug TP (11) or 500 ug DHT with 200 ug TP (177) provided no PEI changes from TP alone. The same lack of change occurred for 21 days pretreatment with 1 mg T before the addition of 1 mg DHT (141).

Similarly, treatment at castration produced no PEI change. DHTP and TP at 100 ug (163) or 75 ug of DHTP plus 150 ug of the synthetic androgen, 19-Nortestosterone, showed no change from TP or intact controls over 21 or 35 days of treatment.

Androsterone (And)

PEI maintenance data appeared in only one study (160) of androsterone. Androsterone propionate (150 ug) showed no change from castrate PEI_1 over five weekly tests. The And/cast. ratio was assumed to be 1.0. The overall And/intact ratio was r = 1.59 (n=5). Unfortunately, no data were available for higher dosages.

Androstenediol (Aeol)

The same researchers (46,157), using different strains, reported data on androstenediol. Inexperienced males were treated at 60 to 120 days postcastration. The earlier study (46) reported no effect on PEI_1 with 1000 ug Aeol compared to the same dose of T over 33 days of injection. The latter study (157) could report no PEI values

for 0.3 and 1.0 mg of Aeol because only one male attained ejaculation. No effect was found for PEI_1 at the 3.0 mg dosage. The Aeol/T ratios fell both above and below the 1.0 value. No explanation of the differing responsiveness to the 1.0 mg Aeol dose was given nor was one readily apparent. No effect on the PEI was assumed for the model.

Androstenedione (Aeone)

The PEI_1 was reported unchanged (46,157) and significantly increased (164) by 1.0 mg Androstenedione under recovery conditions, when compared with the same dosage of T. The average Aeone/T ratio for studies (46,164) with a sufficient number of responding males was r = 1.49. Unfortunately, no time course was given under recovery conditions.

No effect was found for the PEI_1 under a maintenance regime over five weekly tests with 150 ug of androstenedione enolpropionate (160) and over five tests every two weeks with 800 ug Aeone (205). The controls were respectively intact males and males given 800 ug TP. The deviations about the assumed 1.0 ratio were minimal (0.054 ± 0.014, n=10).

Apparently, dosages of at least 150 ug Aeone were sufficient to maintain at least the first PEI at normal intact levels in those males attaining ejaculation. However, waits of 1.5 months or more after castration required Aeone dosages greater than 1.0 mg to return the PEI to near normal levels.

Hydroxyandrostenedione (HAeone)

The PEI effects of 19-hydroxyandrostenedione did not match those of androstenedione under maintenance conditions. Parrott (160) showed an elevation in PEI in the 150 ug HAeone group, that did not occur in the same dose Aeone group. The average HAeone/intact ratio over five weekly tests was r = 1.26 (n=5). No evident pattern of increase over the time of treatment existed. Apparently, the PEI_1 rise must have occurred prior to the first test at 7 days with injection.

The PEI response for Haeone stood between that for intact or TP controls and for castrates given oil; the ratios were closer to the intact than the castrate. The response to HAeone was more variable than for Aeone. The deviations from r = 1.26 were 0.120 $\pm$ 0.049 (n=5), while those for Aeone were 0.054 $\pm$ 0.014 (n=10). A larger variation would be expected as the PEI response deviated from the normal level as the behavior started to decay, indicated by the reduction in the number of males attaining ejaculation (see PE section). The model assumed r = 1.26 for all HAeone treatments.

Androstanediol (Aaol)

The two isomers, 3α- and 3β-androstanediol, affect the PEI similarly. After treatment of 150 ug Aaol at castration (160), the rate of response was extended in time. However, the 3α-Aaol had the stronger effect. The 3β-Aaol had no obvious androgen properties; the PEI was not significantly different from castration alone. The

deviations of the 3α-Aaol/Cast ratio were high (0.283 ± 0.193, n=3) due to the rapid decay of the PEI. The PEI decay with 3α-Aaol was less rapid; the Aaol/Intact ratio was approximated by the equation:

$$r_{PEI} = 0.0123 \cdot AAAOLDI + 1.62$$

The equation established a ratio value of r = 1.706 for the first weekly test (AAAOLDI=7). The PEI ratio rose linearly to the final value of r = 2.05 by the last test at 35 days (AAAOLDI=35). The deviations about the line were 0.114 ± 0.041 (n=5). The high ratio value at the first test (AAAOLDI=7) indicated the PEI was approaching that of the castrate male; the PEI decay was well established. However, note that the PEI was maintained for two weeks longer by the 3α form.

The addition of DHT to Aaol had no synergistic effects on the PEI. The addition of 1.0 mg 3β-Aaol to 200 ug DHTP (12) at 42 days postcastration for 26 days of injection showed a significant rise in the PEI, approximating that of DHTP alone. Although the PEI_1 rise was higher with DHTP alone, it was not significantly more than for the two androgens combined. As nothing was changed within the model by 3β-Aaol, the values for DHT(P) alone would be reported.

Androstanedione (Aaone)

Androstanedione enol propionate helped maintain the PEI when injected in 150 ug doses starting at castration (160). However, the PEI_1 still tended to increase over the period of treatment, so Aaone was not fully effective. The rise in the Aaone/intact ratios

for PEI_1 was linear:

$$r_{PEI} = 0.0125 \cdot AAONEDI + 1.0 \text{ ; when } r_{PEI} > 1.0$$

The rise was slow and began at intact levels (r=1.0). The PEI values might plateau beyond the 35 days of treatment reported in this study, or it might continue to rise to the castrate level with prolonged treatment. Neither possibility was demonstrated, but for the model the ratio was allowed to continue the rise with prolonged treatment, because some PEI decay was indicated by the decreasing number of males ejaculating over the course of treatment.

19-Hydroxytestosterone (HTP)

The PEI was maintained by 150 ug of 19-hydroxytestosterone (159). No consistent change from the 1.0 ratio (HTP/intact) occurred on three tests during 35 days of injection. The small deviation (0.065 ± 0.013, n=6) from 1.0 indicated a very stable relationship.

When 100 ug of HTP and 100 ug of DHTP were given in conjunction, the effectiveness of the HTP was reduced (163). The HTP+DHTP/intact ratio rose from r = 1.0 to r = 1.176 (n=3). The overall ratio for 200 ug DHTP from the same study was r = 1.745 (n=3). The effectiveness of either androgen in maintaining the PEI tended to average when combined, providing a ratio between the independently treated androgens, indicative of a competitive rather than an additive or synergistic effect. The increased PEI was stable over time, as indicated by the low deviations (0.066 ± 0.031, n=3).

Androgen Summary

The comparative effectiveness of the various androgens was best seen under the same treatment conditions. Parrott (159,160,163) had reported sufficient data under a maintenance regime at dosages approximating 150 ug to make solid comparison possible. The PEI for intact or TP treated castrates served as the baseline (r = 1.0). The normal castrate PEI rose exponentially from the day of castration onward. The effectiveness of any androgen in maintaining the PEI was demonstrated by its ability to retard the PEI rise postcastration or to prevent the rise completely, remaining at intact levels.

Androstenedione and HTP, as well as androstenediol, were effective in keeping PEIs at intact or TP castrate levels (46,157). Androstanedione and 19-hydroxyandrostenedione were less effective. Higher PEI rises were seen with DHT and 3α-androstanediol; even though PEIs rose to a high level with these two androgens, the response was maintained longer than occurred for castrates. The ineffective androgens, having PEIs equivalent to castration alone, were androsterone and 3β-androstanediol. Unfortunately, little was known of how the androgens would perform under recovery conditions. The DHT(P) data indicated the PEI response would attain very similar levels in either regime. Therefore, the androgens of high and medium effectiveness might potentially produce the same level of PEI response under recovery when given for prolonged periods.

5.25 Endocrine Glands - Adrenalectomy

Removal of the adrenal glands from intact males did not affect the duration of the PEI (48). Over 7 repeated tests to 20 days following adrenalectomy, no significant alteration of the PEI was seen.

The same lack of effect of adrenalectomy was seen in castrate males given increasing doses of TP (7-28 ug/100 g BW) using a recovery regime (48)(r = 0.989) or given 150 ug TP using a maintenance regime (82)(r = 1.008 & 0.819). The lack of effect was also assumed for castrate males given 150 ug EB (82)(r = 1.157).

Block and Davidson (48) did report a drop in PEI in adrenalectomized and castrate males compared with castrate males, but the drop was nonsignificant (r = 0.781). The drop was highly questionable as the number of males attaining ejaculation decreased rapidly following castration. However, because the lack of overlap of the standard errors and means between the two groups indicated an actual effect might have existed, the combination of castration and adrenalectomy was given a PEI ratio of r = 0.80 within the model.

5.26 Drug Effects

Several drug groupings were provided with PEI data. Fluoxymesterone was an androgen analog, the anti-androgens were represented by cyproterone acetate and flutamide, and the anti-estrogens were represented by MER-25, cis-clomiphene, and ICI-46474. The drugs inhibiting the aromatase conversion of testosterone to estradiol were metopirone and aminoglutethimide. All anti-androgens, anti-estrogens,

and aromatase inhibitors were tested in combination with injection dosages of testosterone sufficient to maintain sexual behavior at normal intact level in castrate males. The effectiveness of the inhibitory drugs was determined by the comparison of the drug plus T treated groups with those given T but not the drug. Fluoxymesterone was injected alone and compared against a separate testosterone group.

Fluoxymesterone (FM)

Vomachka (198) provided the only data on the effect of FM on the PEI. All treatment groups were previously maintained on 500 ug TP. The males were either in a penile nerve cut group or a sham group that had been repeatedly tested prior to the start of the 500 ug FM treatment.

After the maintenance TP was stopped and the FM started, the PEI values increased compared with the same dosage TP control group. The increase in the FM/TP ratio continued until approximately 35 to 40 days of treatment, where the PEI ratio steadied about r = 1.60 until the final test at 56 to 57 days of injection. The change over days of treatment was fitted to a sigmoid curve with a midpoint at 21 days of injection.

$$r_{PEI} = 0.60 \cdot {}^{1}/_{(1 + (21/DYFM)^{4.5})} + 1.0$$

The equation-curve started at r = 1.0 at the start of treatment (DYFM=0), accelerated up to 1.30 by 21 days treatment (DYFM=21), and decelerated approaching the maximum ratio of 1.60. The rate of change was controlled by the exponent (4.5). The rise in PEI_1

values was very similar in pattern to the rise with oil treatment, that followed the PEI rise seen for castration. However, after the initial rise, the oil treated males could not maintain the PEI even at the higher level. Only one male had a demonstrable PEI_1 by 21 days of oil injection. The FM males continued to demonstrate PEI responses in the majority of the group (n=8) to the end of testing (DYFM=56).

The FM/TP ratios for the penile nerve cut (PNX) males also increased, but no consistent pattern was discernible. The FM-PNX ratios varied about the average r = 1.27 (dev. = 0.139 $\pm$ 0.037, n=5). Furthermore, PEIs terminated by the seventh test (DYFM=35).

The deviations from the model ratios for the FM sham group were similar to those for the FM-PNX group. The sham deviations were 0.145 $\pm$ 0.048 (n=10). However, the sham deviations were separable into those on either side of 21 days of treatment; the variation was greater after 21 days (0.238 $\pm$ 0.077, n=5) than up to 21 days (0.052 $\pm$ 0.012, n=5). The higher variation about the model ratios during the earlier days of treatment indicated the PNX group PEI response was showing signs of decay much earlier than the sham group. The PEI decay started later for the FM sham males as indicated by the higher variation after 21 days of injection, as well as, the higher FM/TP ratio.

With consecutive PEIs, the response to FM differed. No rise in PEI_2 values occurred in the FM sham males; no FM-PNX males were responding by PEI_2. The FM/TP sham ratios fluctuated about r = 1.0, unlike the sigmoid rise that occurred for PEI_1. The deviations (0.149 $\pm$ 0.041, n=7) for PEI_2 were in the same range as for PEI_1, so the lack of change during PEI_2 was not due to the vagaries of wild fluctuations. However, the small number of males responding on

the PEI_2 (n=1-3 males) may have been a contributing factor.

To reiterate, FM treatment resulted in a rise in the PEI_1, but not the PEI_2, following a sigmoid curve paralleled at a higher FM/TP ratio by the FM-PNX males, but for only a short duration of treatment. The rise was very similar to that for castrate males, but the FM maintained PEI_1 and PEI_2 responses far longer than oil controls that approximated castration.

The concept of behavioral decay was well demonstrated by the PEI response to FM. Decay implied a gradual degenerative change in response rather than the presence or absence of response indicative of a threshold. As the cessation of ejaculation approached, the PEI_1 became more variable, as well as increasing compared to the control. For sham FM males the initial PEI rise showed little variation, but later during the plateau phase, the variation was much greater, at the same time as the number of males responding in the group was slowly decreasing. The FM-PNX group demonstrated its decay earlier with an immediately higher ratio and high variation. The sham FM PEI_2 response was of higher variation earlier in treatment, and the response disappeared earlier. However, the lack of change in FM PEI_2 did not follow previous patterns of parallel effects across the consecutive PEIs. To completely fit the decay ideal, the PEI_2 should have shown an increased ratio along with its higher variation.

Cyproterone Acetate (CYA)

The injection of 10 mg of the anti-androgen, cyproterone acetate, into intact (49) or TP (100 ug (49) or 150 ug (204)) treated

males produced no change in the PEI. The TP+CYA/TP ratios ranged from r = 0.807 to r = 1.132, all statistically nonsignificant.

Only in castrated males did CYA have an effect. CYA reduced the postcastration rise in the PEI (49). The ratio (CAST+CYA/CAST) was r = 0.724, and the difference was statistically significant. The castrate males given CYA were nearly equivalent to castrate males given TP (r = 0.977), a definite indication of some androgenic or estrogenic effect of the CYA alone.

Unfortunately, the time course of the effect for castrates was not available; only an average values was given for each treatment group. The model reported no change for CYA in conjunction with testosterone, but did return the r = 0.72 alteration of the castration pattern.

Flutamide (FL)

Like CYA, the anti-androgen, flutamide, had a notable lack of effect on the PEI. When FL was injected (25 or 50 mg/kg BW) into intact, castrated or 100 ug TP treated castrate males (180), no alteration from their like controls occurred. Under a recovery regime, the sexually experienced males had E/C ratios ranging from r = 0.938 to r = 1.085. Flutamide, a nonsteroidal androgen, did not show any androgenic or estrogenic effects in castrate males, as occurred with CYA.

MER-25

The first anti-estrogen under consideration, MER-25, was given in conjunction with 1.0 mg T. Beyer *et al.* (47) treated inexperienced

males under recovery conditions (DPC=60) with 2, 8 or 28 mg of MER-25. No changes in the PEI_1 were found for any dosage, compared with the T controls. MER+T/T ratios ranged from r = 0.948 to r = 1.034.

When 10 mg MER-25 was given in conjunction with DHTP (200 ug), to experienced males, again, no effect was found (12) when compared to DHTP alone (MER+DHTP/DHTP = 1.144). In addition, both the DHTP and the MER + DHTP groups were significantly different from the 200 ug TP control group.

cis-Clomiphene (CLOM)

Like MER-25, cis-clomiphene was ineffective in significantly altering the PEI_1 when given with T. Beyer et al. (47) gave 0.25 and 1.0 mg of CLOM under recovery conditions over a 21 day period. The CLOM/T ratios were r = 0.916 and 1.066 for the low and high dosage of CLOM, respectively.

ICI-46474

The final anti-estrogen under consideration, ICI-46474, was no more effective in altering the PEI than the others (47). The ICI+T/T ratios for dosages of 0.1 or 0.3 mg/kg BW (approximately 0.04 & 0.12 mg/rat) were r = 0.975 and r = 0.966, respectively. ICI deviated from the previous anti-estrogens in eliminating ejaculations with the highest dosage of 1.0 mg/kg BW (0.40 mg/rat). Any PEI changes were thus truncated. PEI did not appear to change up to the point of the

elimination of ejaculation.

Metopirone (MET)

Beyer et al. (47) also studied aromatase inhibitors. Metopirone was given every 12 hours for 96 hours starting one hour before the single injection of 6 mg TP. A MET dose response was indicated for the PEI_1, although the largest change was not statistically significant. The MET+TP/TP ratio rose from r = 1.042 at 10 mg MET to r = 1.433 with 22 mg MET. Under most conditions a ratio of 1.43 would be significant, but as the number of males responding (4/10) was small, the PEI values did not attain statistical significance. The model included a linear dose response for MET, as the one high ratio was suffi-

$$r_{PEI} = 0.036 \cdot DMET + 0.64 \text{ ; when } r_{PEI} \geq 1.0$$

ciently compelling, especially since the increase with increasing dosage was in the expected direction for an interference with the action of TP.

Aminoglutethimide (AGT)

The effect of the aromatase inhibitor, aminoglutethimide, was a major one, but irrelevant to PEI. Dosages of 5.0 and 15.0 mg of AGT combined with the one injection of 6 mg TP (47) completely eliminated ejaculation. The elucidation of any PEI effects was thereby blocked. To demonstrate any potential effects on the PEI, lower dosages would have been required.

Drug Effects Summary

The androgen analogue, fluoxymesterone, was partially effective in maintaining the PEI in castrated males after the removal of TP maintenance. The PEI was not maintained at normal levels, but the behavior was sustained longer than the equivalent of castration. As FM was proposed to act as a peripheral androgen, the extension of the PEI was likely due to the maintenance of penile sensitivity. This was corroborated by the more variable, short effect of FM on the PEI in penile cut males. The FM-PNX males approximated the castrates.

Neither of the anti-androgens, CYA or FL, altered the PEI response of males given systemic testosterone. The lack of effect was unlikely due to insufficient dosage as 10 to 25 mg was substantial, and the dosage of TP was reasonably low (100-150 ug). However, CYA did inhibit the increase in PEIs following castration, somewhat. CYA undoubtedly had some androgen properties.

The anti-estrogens; MER-25, cis-clomiphene, and ICI; were all unable to alter the PEI. However, the PEI duration did not show the decay that occurred with castration, the minor androgens, or FM. The PEI did not rise before it was eliminated by the failure to ejaculate.

The aromatase inhibitors were most effective in interfering with testosterone maintenance. Metopirone caused an increase in the PEI usually seen as the PEI decayed. AGT was effective in eliminating the PEI because it eliminated ejaculation. Any alterations of PEIs at lower AGT dosages was unknown. The aromatase inhibitors were given in conjunction with an unusual testosterone treatment, a single injection at high dosage (6 mg). The procedure may have made the

drugs appear more effective than they would under repeated injections of a lower dose of TP.

5.27 PEI Composite

The postejaculatory interval was a stable measure of sexual behavior. Its stability was demonstrated in its resistance to change from normal durations and in its patterned changes with treatment, when change did occur. The PEI E/C ratios changed less than other behavioral measures due to both the large numerical size when expressed in seconds and the low inherent variability of the PEI.

The PEIs resistance to change was expressed in the number of experimental treatments failing to produce any consistent alteration. the majority of treatments (55.4% - see Appendix C) showed no change. the remainder showed either an increase (33.7%) or a decrease (12.0%) from normal PEI durations. Almost all of the experimental treatments referred to PEI_1 alone, as the first PEI was usually the only one of the five consecutive PEIs reported in the literature.

However, consistent effects on consecutive PEIs were demonstrated in variables determining normal behavior. These included the intrinsic variables (e.g., Age, Strain, or TDN) and independent experimental variables (e.g., TBT, sexual experience, raising condition). Within all these variables, the experimental PEIs and control PEIs showed parallel increases with consecutive PEIs. The PEIs for young and old males, although higher than normal adult males, had parallel age patterns from one consecutive PEI to another. The parallel increases were also seen for the comparison of

day and night testing times. No effect on the PEI was seen for sexual experience or raising condition. Finally, the increase in PEI due to the decreasing time between tests (TBT) was similar between PEI_1 and PEI_2.

Where changes in the PEI were demonstrated, the direction of change was related to the type of treatment. As the value of the experimental variable moved outside the "normal" range, PEIs tended to increase in relation to the distance removed from the "normal". As the age of the test males diverged from the adult range (145-450 days), the PEI increased; the PEI increase was exponential with approach to puberty and with increasing old age, the increase was linear. When the hour of testing (TDN) diverged from 5 hours into the dark phase or occurred in the light phase, the PEI increased. Similarly, forcing fewer days between each test lengthened the PEI.

Mild experimental stimulation tended to decrease the PEI. Enforcing an interval between intromission(s), replacement of the original test female with a new one at satiety (no effects at each E), mild electric shock, and conditioning to attain access to the female, produced a decreased PEI.

However, more drastic or potentially debilitating treatments, such as electroconvulsive shock, conditioning to noxious stimuli (e.g., a loud bell) proved to increase the PEI. The same held for the removal of sensory input. Olfactory bulbectomy or peripheral anosmia and sectioning of penile nerves increased the PEI. The exception was the statistically nonsignificant decrease due to blinding.

In all cases where a hormonal treatment effect was evident, the

PEI was increased. Castration, the injection of low dosages of testosterone or estradiol, or any reported dosage of DHT(P) produced increased PEIs. The postcastration exponential rise was the most prominent and served as one base of comparison for other hormones. Several lesser androgens also produced increased PEIs, varying from the more effective androstanedione, producing the least change from intact PEIs, to androgens (And & 3β-Aaol) approximating the castration increase.

The PEI response to many hormonal treatments had the appearance of a decay phenomenon. The changes due to the time of treatment, lower dosages, or comparison of the effectiveness of similar hormones at the same dosage were to increase the PEI and increase the variability in the male group PEI average reported. A decay process does have the same characteristics of increasing variability and deviation from the "normal" state. The changes in PEI over the days of hormone injection developed gradually and appeared as males within the treatment group ceased ejaculation. The PEIs tended to increase as did the variation in PEI values until the PEI measure dropped out completely with the cessation of ejaculation in all males. Of course, the later successional PEIs dropped out before the PEI_1. Perhaps, the lack of change of PEIs following PEI_1, when changes did occur in the PEI_1, was due to the elimination of later ejaculations before any decay effects could be seen. This indicated the possibility that the mechanisms controlling PEI were more resistant to hormonal deficiencies than those controlling ejaculation.

The presence of a noticeable PEI decay effect was related to the degree of peripheral maintenance of penile structure. Castration

provided a clear example. Immediately following castration, testosterone blood levels fell rapidly to nondetectable levels by one to two days (see Testosterone section). However, influence of the prior T continued longer at the penis; the penile papillae, important for sensory stimulation, did not start to regress until about six and one-half days after castration. The papillae approached the regressed state of long-term castration by 8 to 10 days after castration. Under these conditions following castration, the decay of the PEI was pronounced.

The PEI decay was also noticeable for the androgens other than T, especially in the case of DHT. When DHT(P) was administered at castration, the PEI rose to a plateau level (r = 1.66) long before the cessation of ejaculation. DHT maintained PEIs at the higher levels for up to 70 days of daily injections. Admittedly, the decrease in ejaculating males was similar between oil and DHT(P) castrates, but DHT(P) did sustain PEI decay effects far longer, probably due to DHT's known ability to completely maintain the penile structure and consequent sensation.

Other systemic androgens allowed the rise in PEI similar to DHT and castration, but to varying degrees. Administration of 3α-Aaol resulted in a PEI rise (r = 2.02) over 35 days of injection. Aaone and HAeone also allowed some PEI rise (r = 1.30), that remained relatively stable from 14 to 35 days of injection starting at castration. Other androgens approximated either the response of castration alone (3β-Aaol, And) or intact males (Aeone, HTP).

The greatest PEI decay was demonstrated with fluoxymesterone (FM), a synthetic androgen believed to act only peripherally. As

described previously, FM maintenance treatment initially resulted in a rise similar to castration, but the PEI was maintained to the end of testing (57 days of injection) at a high level (r = 1.60). In addition, FM treatment demonstrated a clear increase in PEI variability with the prolonged treatment. Both elements of decay were clearly in evidence and again tied to the maintenance of penile sensitivity.

Essentially, PEI decay was observed only when ejaculations were at least temporarily prolonged through peripheral penile stimulation. Hart (92,94) demonstrated that the mechanics of ejaculation were controlled in the lower spinal areas; the ejaculation reflexes remained in spinally transected males. The reflexes were maintained by testosterone and DHT in castrated males. T, DHT, and FM also maintained the penile papillae (see PP and PW section).

Furthermore, PEI change due to sensory manipulations occurred only when not related directly to the control of ejaculation. OBX caused PEI increases, although blinding did not, but neither eliminated ejaculation. However, penile nerve cuts did more to eliminate ejaculation than to stimulate PEI change. PNX caused little PEI change (r = 1.07) in intact and TP castrate males, and in FM-PNX males, ejaculation rapidly disappeared; the PNX-FM/TP ratios did not rise to the level of the sham FM males. Similarly, penile anesthesia resulted in no ejaculation and observable PEI decay, but ejaculation was the prerequisite.

Hormonal effects on the PEI outside those of the gonadal and androgen hormones were scanty. Adrenalectomy had no effect on intact or TP treated males and only questionable effects when combined with

castration. No data were available for the group of nongonadal hormones or other manipulations of the endocrine glands.

Similarly, little was added to the PEI picture by the treatment with anti-androgens, anti-estrogens or aromatase inhibitors. None of the anti-androgens or anti-estrogens produced any significant changes in the PEI. These drugs may have been more effective in eliminating ejaculation than allowing PEI decay effects to appear, or they were just ineffective.

The aromatase inhibitors blocked the testosterone conversion to estrogen, but did not block the conversion to DHT, that would suggest continuance of peripheral sensitivity important for PEI decay. Unfortunately, metopirone had no effect on ejaculation, and the increase in the PEI at the highest dosage (22 mg) was nonsignificant ($r = 1.43$). AGT was highly effective in eliminating sexual behavior at the dosages utilized, but with no ejaculation, PEI changes were impossible. At lower AGT doses (<5 mg), some interesting PEI effects might have been seen. The aromatase inhibitor data were further complicated by the use of a single dose of testosterone. It was unfortunate that the inhibitors were not used to best advantage, as they might well have added further support to the need for peripheral maintenance of ejaculation necessary for the demonstration of PEI decay.

Chapter 6

A Summarization of the Input - Output Variable Relationships

6.1 Introduction

The previous chapter on the PEI measure provided a detailed look at the effects on PEI due to the input variables. The representation of the effects on the PEI by the model values and equations were also discussed. The PEI measure provided an adequate example of the nature of the model and all the subprograms for the output variables. Because a complete discussion of each of the output variables would be exceedingly long, the effects on each of the remaining output variables were summarized.

This chapter provides a summary for each input variable, excluding the PEI. Each behavioral, penile, and hormonal measure has a separate section. Although the discussion of the remaining output variables is curtailed, the details of the calculation of effects of the model and their representation within the model are equivalent to those for the PEI. Appendix C provides a listing of the direction of effects upon each of the behavioral measures, as well as any lack of effect. The behavioral measures; IL,IF,EL,EF,PE,PI,PM; are described first.

6.2 Intromission Latency (IL)

The intromission latency is the first duration measure encountered in the sexual behavior sequence, with the exception of the mount latency that was data poor. The intromission latency (IL) is defined as the time (in sec.) from the introduction of the female to the test arena to the occurrence of the first intromission. Only one IL occurs during a sexual behavior test, regardless of the number of ejaculatory series. An exception is sometimes made for treatments where the female is removed from the arena and later replaced during the ongoing behavior, as occurs for an enforced interval between intromissions (EICI) or during the PEI (EPEI). These "intromission latencies" after the female is replaced are not comparable to the IL at the start of testing. Therefore, any IL values appearing in the model for ejaculatory series other than the first series are these pseudo-ILs. A further exception should be mentioned. When no data were reported for the IL, but the less reported mount latency (ML) was reported, for a particular treatment variable, the E/C ratios for the ML were utilized as a replacement for the IL.

Intrinsic Variables

The extremes of the intrinsic variables tended to increase the IL length. The IL was longer at the younger (140,178) and older (119,132,140) ages, with no significant changes during the adult ages (213-426 days). The increase in IL was exponential as the age diverged from the adult range. Sexual testing during the light phase

of a 24 hour light cycle resulted in a nonsignificant increase (31) in the IL. During the dark phase, the IL was longest near lights-out and shortest near lights-on (63). The linear decrease with increasing TDN (hrs. during day) was nonsignificant. With decreasing number of days between testing, the IL exponentially rose to a maximum E/C ratio of 19.0 at TBT=1 (30,76). The lack of prior sexual experience also resulted in increased ILs; differences were both statistically significant (64,70,169) and nonsignificant (48,159,169).

However, raising a male alone (Isol.)(22,87,184) or with females (Cohab.)(70,184) decreased the IL when compared with males raised with other males (Seg.). The isolate IL was the most affected. The cohabitation condition interacted with the sexual experience variable, as the IL increased with reduced sexual experience. Due to the experience alone the cohabitant males would be expected to show a lower IL than the segregate males. However, there was no obvious explanation for the reduction in the IL of the isolate males. When the experimental male was raised with females, but separated from them by a double wire mesh (SCREEN), these males were comparable to the segregate males (184).

Behavioral and Stimulus Variables

The behavioral treatments demonstrated no consistent pattern of effect. The latencies to intromission, the pseudo-IL ("IL"), reported for enforced intervals between intromissions (EICI) increased with lengthening intervals (39). However, the "IL"

initially fell gradually to a nadir from approximately 1 to 8 minute EICIs (91,130). Although no support was available, the "IL" would be expected to gradually increase with longer EICIs until reaching the level of a normal IL. The number of intromissions allowed prior to an EICI was an additional factor; the more intromissions allowed before the EICI, the greater was the "IL" decrease (39). For the enforced PEIs, the "IL" decreased to E/C r = 0.24 (39,68,126) and started to increase with EPEIs longer than 150 minutes (39).

The replacement of the current stimulus female with a different female (NFRESH) resulted in differing effects on the "IL" at replacement. No change occurred when the original female was replaced with a fresh female after an ejaculation (68). On the other hand, the "IL" increased when replacement was made after the attainment of sexual satiety (44,56). No interaction (44) existed with a EPEI and treatment at satiety.

Electric shock stimulation during testing usually resulted in a decrease in the IL (23,51,52,81,171,173). However, if the level of shock were further increased, the IL increased. The increased shock level was either an intensity change, 100 up to 380 volts (23), or a frequency change, one to ten shocks per minute (52). When a bar press paradigm for access to a female was added to the lower shock condition, the effect of shock was eliminated (173). The stronger effect was the bar press, which increased the IL, washing out any shock effect. Electroconvulsive shock significantly increased the IL washing out any shock effect. Electroconvulsive shock significantly increased the IL during 12 days of daily treatments (26).

Unlike the increase due to the positively reinforcing bar press

paradigm, the IL decreased under a negative reinforcement paradigm, if any change occurred (24,208). The negative reinforcement was a shock given when the male approached the stimulus female. However, if the conditioned males were tested without shock in a novel arena, the effect disappeared (24,208). Apparently, the effect of shock became situational.

The conditioning shock and the shock given to stimulate performance both decreased the IL when testing occurred in the same apparatus as the shock. This conditioning effect, therefore, was confounded between the conditioning and shock stimulus. The primary effect was probably that of shock; the males learned to anticipate the shock in a specific environment, and performed commensurately even when shock was not presented.

Several other stimuli produced differing effects. The fitting of a large collar (96), preventing genital grooming, decreased the IL. Handling the males during testing (132) produced no change in IL in younger males (5-6 mos.), but did produce a nonsignificant increase in the older males (20-25 mos.). When the experimental male was exposed to a copulating pair prior to testing (90), a nonsignificant decrease in the IL occurred, but copulation with a female with a closed vagina (VagX) resulted in no change (88).

Sensory Variables

The sensory manipulations consistently resulted in an increased IL, provided an effect did occur. The removal of the olfactory bulbs (OBX) and surrounding brain areas or peripheral anosmia induced a

questionable increase in the IL. Different studies reported statistically significant increases (45,98,206) and decreases (137), as well as, nonsignificant increases (45,138) and decreases (14,100,168). The overall average was r = 1.76, and because the significant increases were more numerous, the average was adopted. OBX certainly created highly disrupted sexual behavior, because many of the OBX males did not display the behavior (see PEPIPM section).

Blinding altered the IL only in inexperienced males (84,85). Blind males with some prior sexual experience provided just nonsignificant changes (14,89).

Severing nerves innervating the penis also showed experiential differentiation. With sexual experience prior to the penile nerve cuts (PNX), the IL increased five fold over the sham operated control (142,150,198). The males given no prior experience had a substantially larger IL increase (149). No consistent changes over repeated testing were observed in either case. Similarly, the application of an anesthetic to the penis resulted in increased ILs (1,83).

Other manipulations, such as severing the fifth nerve, innervating the snout and vibrissae, resulted in an increased IL (14) as well. However, if more than one sense were interrupted (included OBX, blinding, 5th nerve) no sexual behavior occurred (14), making the IL nonexistent or as long as the test period.

The only attempt to interfere with hearing was a repeated loud bell, which increased the IL six fold; but too few males were used to demonstrate statistical significance (51). Finally, electrical self-stimulation of the hypothalamic "pleasure" area to the point of ejaculation produced no IL change when tested afterward with a female (4).

Hormonal Variables

Like the sensory manipulations, hormonal effects produced only increases in the IL compared with normal intact males. The hormone effects were categorized by gonadal hormones, androgens (excluding testosterone), drugs, and a miscellaneous grouping.

The initial gonadal hormone treatment was castration. Castration resulted in an exponential rise in the IL up to almost a six fold increase over the intact IL (58,60,198,205). The rise began at approximately one and a half days postcastration.

In castrate males, daily injection of testosterone propionate (TP) returned the IL to normal intact duration. Under a maintenance regime, 100 ug of TP was sufficient for normal ILs. At lower dosages, the IL seemed to increase linearly with decreasing dosage (28). No significant changes occurred over the days of injection at the higher dosages (198,205).

Under a recovery regime, a higher sufficient TP dosage was indicated. Extrapolation of the Södersten data (177) indicated a dosage of about 350 ug TP was required to produce a normal IL. Lower doses resulted in commensurately higher ILs. The higher sufficiency level was consistent with other, more limited data (181,144).

The effects of estrogen injection were more difficult to interpret. In castrate males, high EB doses (70-150 ug) apparently maintained normal ILs (59,82). Under recovery conditions, the results were equivocal. The castrate males treated with EB had reported E/C ratios of 0.222 to 5.333 (144,164,166,176,177,181) for dosages of 0.5 to 100 ug. However, a weak trend of increased ILs at

the higher EB dosages was observed.

In intact males, an increasing dosage of EB resulted in increasing IL values (with a decreasing number of males intromitting in one study)(59). However, no statistically significant change in IL with increasing dosage occurred in another study (176). In both cases, the IL was elevated.

Androgens

Dihydrotestosterone (DHT) did not return the IL to intact levels. DHT (500-1000 ug) in castrate males resulted in about a two fold IL increase over intact males (144,164,177,205) under either a maintenance or recovery regime. No change in the IL level occurred over 14 days of injection (205).

When EB (.05-50 ug) was combined with DHT (1 mg), the IL was reported at intact levels (144,198). No obvious change was observed over the EB dose range (144) or over 12 to 40 days of injection (198). If estrone (1-5 ug) was substituted for the same dose of estradiol and combined with DHT (500 ug), the IL was three times longer with the estrone combination (145). Furthermore, the combination of higher doses of DHT (500-1000 ug) with 1 mg T (141) or 200 ug TP (177) kept the IL at normal levels.

Androstenediol (AEOL) was just slightly less effective than androstenedione (AEONE) in returning the IL to normal levels. AEONE effected normal ILs with at least 100 ug dosages (46,157,164) under recovery regimes. At the same dosages, AEOL was slightly less effective, as demonstrated by the ratio of AEOL/AEONE = 1.12 (46,157).

There was no change from the intact IL under a maintenance regime out to 70 days of injection (205). DHT was less effective than either AEONE or AEOL.

Hypophysectomy and Adrenalectomy

Hypophysectomy when combined with castration significantly inhibited the castration IL rise for at least three weeks after surgery (165). Adrenalectomy proved ineffective in altering the ILs of either intact (48) or castrate (48) males, or when castrates were given testosterone (48,82) or EB (82).

Drug Treatments

The nonsteroidal androgen analogue, Fluoxymesterone (FM), did retard the increase in IL following castration or the cessation of TP treatment (198). With FM, a rise in the IL started at approximately 21 days of injection and attained a plateau at a three and on half fold level after 28 days injection. This rise never attained castration IL levels, and the IL rise was maintained well beyond the termination of all behavior following castration. When PNX was combined with FM injections, the effect of FM injection was equivalent to that of TP. The PNX took precedence over any effect of FM (198).

Anti-androgens did not alter the testosterone maintained IL. Cyproterone acetate (CYA)(10 mg) did not alter the IL of castrates (49) or those given TP (49,204). Similarly, Flutamide (FL)(20-25 mg)

injection of intact or TP treated males proved nonsignificant (180).

The IL changes due to anti-estrogens were more pronounced, but inconsistent. MER-25 produced decreasing ILs with increasing MER dosage (2-28 mg) in T injected males, but the decrease was nonsignificant. ICI, however, showed a definite, but nonsignificant, IL increase at the highest dosage (0.1-1.0 mg/kg BW) in T treated males (47). On the other hand, cis-clomiphene (.25-1.0 mg) caused no noticeable change in the IL (47). Overall, a lack of effect of the anti-estrogens must be concluded.

The aromatase inhibitors also proved of no use. They did not inhibit the effect of a single injection of TP (6 mg). Both metopirone (10,22 mg) and androstanedione (2.5-5.0 mg) were ineffective (47). Aminoglutethimide (5-15 mg) had no IL data as the males did not intromit (47). Again, none of the drugs interfered with testosterone action. FM proved to act like an intermediate strength androgen.

Synopsis

When sexual behavior began to degrade, the IL increased, and only decreased in response to non-noxious stimulation. The obvious cases where behavioral degeneration occurred, such as castration or low testosterone dose, resulted in an increased IL. The other androgens and FM demonstrated degrees of IL recovery and maintenance. Estrogen had either no effect on the IL, or insufficient dosages were reported to demonstrate one.

The removal of sensory stimulation, i.e., sensory organ removal,

was uniformly effective in increasing the IL. This was an expected result, as the loss of a sensory modality would be debilitating to some degree. Decreases in the IL occurred for low levels of shock, an "excitatory" stimulus. However, if the intensity of the shock was increased, it became a noxious stimulus, as demonstrated by the increase in the IL. The same held for an ECS. In addition, the lack of adequate sexual experience, very young or old age, frequent testing, or testing during the rat's light period all proved to increase the IL. The extremes of most common variables also appeared to be debilitating.

6.3 Intromission Frequency

The Intromission Frequency (IF) is defined as the number of intromissions occurring during the interval from the first intromission to the ejaculation of each ejaculatory series. The IF is subscripted based on the particular ejaculatory series measured. For example, the first IF (IF_1) for a group of males is the average number of intromissions occurring prior to the first ejaculation, and the intromissions following the first PEI to the second ejaculation is the second IF (IF_2). The numbering continues to sexual satiety or the test termination.

Approximately ten intromissions occurred during the IF_1. The IF_1 study means indicated differences between strains. The Göteborg males had the highest IF_1 of 13.2 ± 0.4 ($n = 23$ studies), and the Sprague-Dawleys had the lowest of 8.6 ± 0.4 ($n = 9$ studies). The remaining strains fell at about 10 intromissions. The range in

the IF_1 reported in individual studies (n=85) was from 6.5 to 20.3.

Over five consecutive ejaculatory series, the IF_1 was the maximum IF. The IF_2 was approximately 50% of the first IF. The IF_{3-5} gradually increased with successive series, at least to the end of the fifth series (30,62,74,102,119,125 - reporting 4 or more consecutive series). The strain differences reversed for IF_{2-5}, with the Göteborgs having the lowest IFs and the Sprague-Dawleys the highest. During the following discourse, the reader should assume no data were available for IF_{2-5} if no mention is made of these series.

The IF changed due to the male rats' age, with the greatest change occurring during the rats' youth. Proceeding from puberty, the IF fell exponentially to adult levels at 165 days of age for all ejaculatory series (64,119,123,128,132,140). Following a stable adult period, the IF gradually decreased, but nonsignificantly, with older age (>312 days for IF_1 & >430 days for IF_{2-5})(70,119,123,132, 140).

The time of testing during the rats' dark hours proved to have no significant effect. However, a nadir for IF_{1-2} was apparent at TDN=4 hrs. (63). Testing during the light phase showed no consistent differences from dark phase testing for IF_{1-5} (31,119,123).

No effect of the test spacing (TBT) was seen for intervals from 90 minutes (44) to 15 days (30,59,119). The lack of effect was maintained over IF_{2-5} (119). Similarly, no effect of sexual inexperience was observed in adult males (48,64,70,119,158). Furthermore, the raising conditions of cohabitation (15,70,87,139,

184) and isolation (15,22,71,87,136,206,208) did not differ from segregation for IF_{1-2}. The introduction of a screen between males or between males and females was also ineffective (184).

Behavioral and Stimulus Variables

The enforcement of an interval between intromissions (EICI) decreased the number of intromissions in an ejaculatory series. With increasing EICI length, the IF decrease was rapid and exponential, and it attained a minimum value by an EICI of 5 minutes. With longer intervals, past 30 minutes in duration, the IF gradually returned to ad lib. values (40,129).

The degree of the EICI-IF decrease could be differentiated by strain. Göteborg males had the greater decrease (65%) for both single (119) and multiple (119,129,131) enforced intervals within a series. The Long-Evans (42,43) and Sprague-Dawleys (91,131) produced a decrease of 42%. The response pattern was evident for all five series (42,119,128,129,131). The response to EICIs was influenced by the number of intromissions (I) allowed prior to the enforced interval; the greater the number of prior Is were, the greater the reduction in the IF (42,129).

Enforcement of an interval following an ejaculation (EPEI) increased the IF of the following series, and the increase grew with increasing EPEI duration. As with the EICI, the EPEI effects could be differentiated by strain. The Göteborg IF increase was slightly more rapid and based on a square root function (121,122,125,130), while the rise in other strains (39,67,68) followed an "e" function.

In all strains, the IF_{2-4} rose to approximately twice their normal value with EPEIs of more than 4 hours. Recalling that the IF_{2-5} was usually one-half of the IF_1 and the EPEIs when sufficiently long approached intervals between tests, the doubling of the IF_{2-5} becoming the IF_1 of a new behavioral sequence of the next test.

No interaction of the EICI and the EPEI was indicated (130) and the multiplication of the model ratios for both EICI and EPEI provided a reasonable IF response. However, the study gave only one manipulation of the EICI variable for a range of EPEI values. The manipulation of both variables in conjunction would be required for a complete test of an interaction.

The exchange of a new female for the original female was ineffective on the IF when the exchange occurred at each ejaculation (6,62,67,68,77,101,102,207). However, when the exchange was made only at sexual satiety, a nonsignificant increase ($r = 1.20$) occurred (56,74,116,207). With a 60 minute EPEI added to the female exchange, the rise in the IF_5 was depressed from the height of the EPEI treatment alone (62).

IF_{1-4} were not affected by the application of shock at low levels (below the pain threshold)(6,23,50,52,81,171,173). However, at high shock levels, the IF_1 was drastically reduced (23). Electro-convulsive shock (ECS) also decreased the IF (26), but to a much lesser extent than the high shock.

The use of shock for avoidance conditioning reduced the IF only when the ad lib. tests occurred in the same cage used for female avoidance training (24,97,208). The testing of trained males in novel cages reduced the conditioning effect (24,208), somewhat. A

one-half reduction in the test arena size decreased both the non-shock and shock groups for IF_{1-2} (50).

Other conditioning paradigms produced increased IFs. When a light (CS) was paired with copulation (UCS), the IF_1 was increased, but not IF_{2-3} (119). Pairing a loud bell (CS) with copulation increased the IF_{1-4}; the greater effect occurred during the IF_1 (119). Training to bar press or pull for access to the female proved ineffective over IF_{1-4} (104,119,173). However, when shock during testing was added to prior bar press conditioning (173), the treatments were synergistic. Neither treatment produced a significant effect alone, but together they substantially reduced the IF_1 ($r = 0.50$).

Testing males and females in groups significantly reduced the IF_1 in males of all ages (119,120). The reduction in IF_{2-5} was far less, but the reduction was greater in the older males (25 mos.)(119). The reduction was even less when the three male-female pairs were tested in three adjacent arenas simultaneously (119). Handling the male during testing also reduced the IF, but only in old males and only for the IF_1 (68,132).

Some stimulus object manipulations reduced the IF. Exposure of males from 37 days of age to a receptive female or another male in a testing arena reduced the IF_1 as adults compared with males given no early exposure (105). The sexual stimulus of a nonreceptive female, a young male, an immobile estrus female, or a small guinea pig resulted in no display of the intromission pattern by inexperienced male rats (13,14,17). McLean et al. (156) reported an interaction among female stimulus rats from different strains. The Long-Evans female was the most preferred and the Wistar female was the least

preferred by all males. The Long-Evans males were the least discriminating among the females. In general, males preferred females of other strains. However, the data for intromissions was reported as total Is/30 min. test, not as IFs, and the totals were unusually low.

Males given 40 minutes with a vaginally closed female prior to sexual testing had significantly reduced the IF_1 (88). Exposure to a copulating pair for the same time had no effect on the IF_1 (90), and neither did the wearing of a long collar to prevent genital grooming affect the IF_1 (96). Similarly, electrical brain self-stimulation had no effect (38,55).

The IF was not particularly sensitive to the behavioral and stimulus treatments. Shock designed to arouse the male proved ineffective, as did providing a new stimulus female, except at satiety. The EPEI forced the IF to return to levels approximate to those at the beginning of a new test when the EPEIs were sufficiently long. However, when effects on the IF did occur, they were usually decreases, such as for group testing, access to a VagX female, avoidance conditioning, high shock, EICI, ECS, half sized arena, and sexual stimuli other than the normal receptive female.

Sensory Variables

The interruption of sensory input to the central nervous system tended to decrease the IF, at least, due to the removal of stimulation from the nose or penis. Blinding was ineffective.

Olfactory bulbectomy (OBX) did lead to decreases in the IF for

both sexually experienced (14,98,100,137,138,196,206) and inexperienced (14,139,168) male rats (r = 0.86). Males made peripherally anosmic, without brain injury, were comparable to the OBX males (138).

Several manipulations of sensory input from the penile area were attempted. Anesthesia of the penis either eliminated intromission (53) or interfered (1) with its display. Removal of the penile bone greatly reduced the IF (27). Severing the nerves innervating the penis inconsistently affected the IF_{1-3} (142,198) of those experienced males that responded; no clear change was evident. The only potential exception was an enhancement of the effect of castration (198). In any case, intromissions did disappear by the third series in PNX males castrated and injected with TP or FM (198).

Neither blinding (14,89) nor severing the facial nerve (14) affected the IF. However, if two or more sensory modalities were eliminated, all the males failed to achieve intromission (14).

Hormone Variables

Castration caused a decrease in the IF. A decrease to 60% of normal intact levels in IF_{1-3} (49,58,59,159,162,165,188,198) was evident by 6 to 7 days postcastration, and was maintained to at least 35 days postcastration. However, no pattern of decrease immediately following castration was provided. Castration was the precondition for almost all the following hormonal treatments.

Testosterone treatment effected no consistent changes after seven days with injection under either the recovery (136,165) or maintenance (159,198) regimes using 75 ug (159) or approximately 500

ug (136,165,198) T or TP. A dose response became evident only with less than 100 ug or less than 5 mm lengths of T filled, silastic implant. An exponential decrease in the TTP/intact ratio for the IF_1 was indicated with a 2 mm silastic implant (57) and by 50 ug TP or less (28,177). The exponential coefficients for the two delivery systems gave a relationship of 14.7 ug TP for each millimeter of T implant. A single injection of TA (10 mg) maintained normal IFs for nearly 8 weeks, twice that for TP at the same single dose (33).

The IF responses to estradiol (EB) were difficult to interpret. No single study provided a dose response relationship. Södersten (176) reported no change from the castrate IF for 5 to 200 ug/kg BW. Similarly no consistent change over dosages of 0.5 to 70 ug EB generated from several studies (11,59,144,164,166,176,177,181,198) was evident. The variability in the IF ratios (EB/TP r = 0.26 to 2.26) was very high, with a majority of the high ratios at the 5 ug or less dosages. A major problem was the low number of males responding to the EB (the IFs were based only on the responding males). Possibly, when sexual behavior degenerates, the IF increased in some males and decreased in others before intromissions disappeared, thus accounting for the high ratios in some groups and low ratios in others with little regard for dosage. The model assumed an increased IF for the lower EB dosages.

The IF tended to decrease over days of treatment (5,59) with high EB doses (70 ug & 100 RU) under maintenance regimes. With a recovery regime, 100 RU of EB increased the IF from castrate values (5). However, all results for EB should be viewed with skepticism due to the inconsistency among studies. The IF was consistent with a normal IF when 1 ug EB was combined with TTP (141,177).

Androgen Variables

The limited data on dihydrotestosterone (DHT) effects on the IF provided no indication of changes. Under a recovery regime, 200 to 1000 ug of DHT(P) showed no consistent change from normal, intact IF_1 (12,144,152,164,177). Maintenance with 150 ug DHTP (159) resulted in a possible IF_1 decrease. In addition, combinations of 200 ug DHT(P) or more with 1 to 50 ug of EB (11,144,152,198) or 200 ug TTP or more (143,177) kept the IF_1 at normal levels.

The effect of androstenediol (AEOL) or androstenedione (AEONE) on the IF_1 proved an all or none response. Both no intromission (157) and a normal IF (46,164) for both androgens occurred with a recovery regime. The lack of intromission occurred up to the 1 mg dosage. AEOL tended to be more able to induce intromission than AEONE (157).

A 19-Hydroxytestosterone (HTP) injection (150 ug) under maintenance conditions had inconsistent results over the five weeks of injection (159). One experiment showed a nonsignificant increase for IF_1 over the five weeks. However, a replicate experiment had a significantly reduced IF_1 at the first week and no intromission by the third week, which approximated the response of the oil injected castrates.

Overall, the studied androgens were not particularly effective in demonstrating significant changes in the IF. Intromissions tended to disappear before any consistent change in the IF occurred.

Other Hormone Variables

Adrenalectomy did not alter the IF, regardless of whether males were intact, castrated, or given TP (48). The addition of progesterone to EB (7,166) or TP (166) caused no further changes. Also, LH plus FSH in castrate, hypophysectomized castrate (165), or OBX males (137) caused no significant changes from the control IF.

Drugs

The IF resulting from fluoxymesterone (FM) injections deviated from normal levels only when penile nerve cuts (PNX) were combined with the FM (198). No consistent deviation in IF_{1-3} occurred in sham males given 500 ug FM under a 57 day maintenance regime. The FM-PNX males showed a consistent, increased IF_1 ($r = 1.48$), with no pattern of change after 4 days with injection (198). The combination of FM and EB (50 ug) increased the number of intromissions over those for castrate males (103).

Anti-androgens had some effect on the IF of intact males and equivocal effects on castrate males. Cyproterone acetate (CYA) produced a nonsignificant increase in castrate males (49,152), but produced no change in TP injected males (49,204). Flutamide (FL) caused nonsignificant decreases in intacts, castrates, and TP injected castrates (180).

None of the anti-estrogens studied indicated any change of a TP replacement IF. The drugs included MER-25 (47), CI-628 (202), cis-clomiphene (47), and ICI-46474 (47). Similarly, MER-25 (10 mg) with

DHTP did not differ from DHTP alone (12).

The aromatase inhibitors, like the anti-estrogens, proved ineffective in influencing the IF in TP treated males. Several milligrams of metopirone, aminoglutethimide, or androstanedione did not alter the IF of responding males (47). However, AGT eliminated intromission at both 5 and 15 mg dosages (47).

Overall, neither the anti-androgens, anti-estrogens, nor the aromatase inhibitors significantly altered the IF. However, IF decreases were seen with CYA, FL, Metopirone, and AGT. The reality of these decreases has remained in question, particularly, because some of the drug and concomitant control treatments reduced the number of males attaining intromission.

Synopsis

The IF remained relatively unperturbed by any experimental treatments. When changes did occur, the IF was depressed in the majority of situations, such as the manipulations of behavior and sensory input. The variables effecting increases included young age, a fresh female at satiety, EPEI, two types of classical conditioning, and response to EB, TA, and a couple of TTP paradigms. On the whole, the IF provided no discrimination among the different variable classes, with the possible exception of a relative lack of response to the drugs. The IF was apparently either a very stable measure or so variable that differences could not be statistically established until the entire pattern of the sexual behavior began to degenerate. When IF changes did begin to appear, there was no consistent means of

ascertaining whether the IF change would be positive or negative.

6.4 Ejaculation Latency

The ejaculation latency (EL) is defined as the time (in seconds) from the first intromission to the ejaculation of each ejaculatory series. Each successive EL is subscripted according to the particular series. The first EL (EL_1) is the longest, followed by the EL_2, which is usually the shortest. Continuing from the EL_2, the ELs increase with each successive series, at least to the fifth EL. In addition, the increase is greater with each successive EL.

The EL_1 differed among the various rat strains. The Göteborg had the shorter EL_1 at 398 $\pm$ 38 sec. ($\bar{X} \pm SE$)(n = 9 studies). The Long-Evans with an EL_1 of 480 $\pm$ 40 sec. (n = 15 studies) fell in approximately the same range as the Wistar males at 466 $\pm$ 107 sec. (n=8). The higher EL_1 durations were from the Sprague-Dawley males at 590 $\pm$ 57 sec. (n=5) and the mixed grouping at 590 $\pm$ 59 sec. (n=10).

The EL was affected at both very young and older ages. EL_1 followed an exponential rise preceding from about 200 days of age toward puberty (119,128,140). This pattern was repeated across all five series (EL_{1-5}). The pattern of change in the older males (>600 days) was more gradual; it appeared linear (119,124,132,140). The old male pattern also was maintained over consecutive series, with some decrease in the rate of increase with age due to increasing series.

The EL was altered during the rats' light cycle. EL_{1-2} were highest when the dark phase began and decreased exponentially to

their shortest duration by the end of the dark period (63). When testing occurred during the light phase, EL_{1-5} was consistently longer (r = 1.67) than the congruent hour during the dark phase (119,123).

Reducing the number of days between consecutive sex tests increased the duration of the El_{1-3} when the testing intervals were three days or less (30,76,119,121). These males were tested to at least three ejaculations.

To some extent, repeated testing, resulting in greater sexual experience, decreased the EL. The increased EL_{1-5} (r = 1.60) due to sexual naivety was inconsistent. Most studies reported increases (48,64,70,127,158,169), but statistically significant effects were rarely found. Any noticeable difference between the inexperienced and experienced males was gone after three sexual tests.

The condition of caging from weaning had little effect. Cohabitation produced no effect on the adult EL_{1-2} (70,87,184). Isolation, especially at Day 2 of life, resulted in some EL_1 reduction; however, the reduction did not attain statistical significance (87,184). Separating the experimental males by a screen from a female had no effect, but when males were separated from another male, a decrease in the EL_1 occurred (184).

Behavioral and Stimulus Variables

The introduction of an enforced interval during sexual testing usually produced an increase in the EL. Enforcing a one minute interval between intromissions (119,130) tended to increase EL_{1-4},

but no evidence of statistical significance was given. The model assumed an increase (r = 1.37).

An enforced PEI substantially increased the EL. EL_{2-5} increased with increasing EPEI, logarithmically, to durations comparable to a normal EL_1 and above (39,67,68,121,122,125,130). Again, the extended EPEIs were consistent with the short intervals between separate tests. In general, El_1 values were attained by EPEIs of 30 minutes or more. EL lengths 50% greater than the EL_1 occurred with EPEIs of 24 hours or more. No interaction of the EPEI with the introduction of a fresh female was reported (67,68).

The introduction of a fresh female after each ejaculation (62,77,101) tended to decrease the EL (r = 0.85). However, changing the female after a single ejaculation provided less consistent results (67,68). Furthermore, introducing the new female only at satiety failed to influence the subsequent EL (45,56,74,77).

A shock stimulus produced significant decreases in the EL length. The effect was less pronounced after the first EL in sexually experienced males. The EL_1 ratio (shock/NS) average (r = 0.59) had great consistency across studies (6,52,81,171,173). The ratio (r = 0.75) for EL_{2-3} (6,52,171) was less consistent. When electroconvulsive shock was used, the reduction in the EL was very similar (r = 0.69)(26). The addition of a bar press for access to the female tended to eliminate the effectiveness of the light shock (173).

Some evidence was available indicating an effect on the EL due to avoidance conditioning, but no effect was evident for positive reinforcement paradigms. A loud bell, a negative reinforcer, paired to mounting (119) significantly increased EL_{1-4}. However, presenting

a shock as an avoidance stimulus to copulation resulted in a decreased EL ($r = 0.83$) when testing took place in the conditioning cage without shock. When testing occurred in a novel arena, the effect of prior shock conditioning disappeared (24). The conditioning was situation specific. The loud bell apparently disrupted ongoing sexual behavior to result in a lengthened EL, but the anticipation of shock effectively produced a facilitation, a reduced EL. On the other hand, a bar press for access to a female, a positive reinforcement paradigm, produced no change in EL_1 (173). Furthermore, the bar press paradigm insulated against the effect of ongoing shock.

Testing multiple males and females as a group (3 pairs) substantially reduced EL_{1-3} of both adult and old males (119). The effect tended to disappear for EL_{4-5}. The same effect occurred, but to a reduced extent, in copulating pairs tested in adjacent arenas (119). The group testing effect was eliminated if testing occurred during the rats' light phase (120).

Other manipulative treatments proved ineffective. Electroejaculation prior to testing (4), prior electrical brain stimulation (55), and long collars (96), preventing genital grooming, were all ineffective.

On the other hand, some stimuli did shorten the EL. Handling the male during testing reduced the EL_{1-3} (132), but the effect was more pronounced and statistically significant for the old males (20-25 mos.). Both exposure to a vaginally closed female (88) and exposure to, but no contact with, a copulating pair (90) for 40 minutes prior to testing significantly reduced the EL_1.

In general, environmental and sexual stimuli depressed the EL. The change to a new female at each ejaculation, shock during testing or conditioning to a "shocking" environment, electroconvulsive shock, group testing, handling, or exposure to incomplete sexual stimuli, all decreased the length of the EL. Only enforced ICIs or PEIs and the conditioning to the negative stimulus of a bell proved to increase the EL.

Sensory Variables

Unlike the effects of sexual and environmental stimuli, removal of a sensory organ or disruption of sensory input consistently increased the EL duration. Olfactory bulbectomy (OBX), blinding, and removal of penile sensation had an inhibitory effect, an increased EL.

The elongation of the EL due to OBX was large. The response ratio (OBX/sham r = 3.60) for EL_1 was definite for experienced males (45,98,100,137,138) and indicated for inexperienced males (206). Additionally, a lessening of the OBX effect was indicated over consecutive ejaculatory series (45). Blinding the males increased the EL_{1-2} (r = 1.86)(89), but not as substantially as OBX.

Reduction of penile sensation also elongated the EL. Removal of the glans penis (183) significantly increased the EL_1, while penile anesthesia (142) eliminated ejaculation and, therefore, the EL.

Severing nerves innervating the penis and genital area (PNX) produced the largest EL increase in sexually experienced males. The

EL_1 rose to three times normal value when the dorsal penile nerves (142,198) or the pudendal nerves (118) were sectioned. A decreasing effectiveness of the PNX was demonstrated (198) with consecutive ejaculatory series, reaching normal durations by the EL_3. However, ejaculation was virtually eliminated by the third series.

Hormone Variables

Castration produced a gradual and approximately linear increase in the EL_1 (59,198,205) with increasing days postcastration. Possibly, this effect was present only for the EL_1. Some data (198) showed no change from control levels for EL_{2-3}, but very few males attained ejaculation in these latter series. A secondary factor, the age at castration, further increased the EL_1, as the age of castration decreased from about 13 days of age (133,135).

Testosterone injection (50-3000 ug) of castrates reportedly induced intact ELs. No data for less than 50 ug were available to establish a dose response for the EL. Recovery was complete with 50 to 1000 ug TP (177) or 300 to 3000 ug T (157). Similarly, dosages of 2 to 60 mm length silastic implants of T (57) maintained the EL at intact levels. No change was seen over 70 days of injection (198,205) under a maintenance regime at higher TP doses ($\geq$ 500 ug). A single injection of TA (10 mg) maintained normal EL values out to 8 weeks postinjection, but TP (10 mg) maintained EL to only 3 weeks (33). The EL was highly responsive to testosterone, as other behavioral measures showed changes at the same low dosages.

Estrogen was less effective than testosterone. The estrogen

data were highly inconsistent, and comparisons with castrated male controls were rare (no doubt due to the lack of behavior). No data were available giving a dose response. Different dosages from different studies had no observable pattern. From 1 to 100 ug EB, the EB/TP-intact ratios varied from 0.94 to 2.28 (11,59,82,164,176, 177,181). There was some tendency for low doses (1-2 ug) to have higher ratios, and for experienced males to have lower ones. The average ratio (r = 1.52) was assumed for EB injections.

Some EL increase over days of injection with EB starting at castration was shown (59), but the most noticeable rise in the EL occurred in intact males injected with EB. The intact EL rose to four times normal with 50 ug EB, and the EL was eliminated with 200 ug (56).

Insufficient evidence was available to conclude the injection of high EB doses was analogous to castration in intact males, or that EB injection of castrate males ameliorated the effect of castration. However, the report of a few EL values under a recovery regime with EB (11,164,176,177) indicated the effect of castration was reduced, because no control males were ejaculating at the later times postcastration.

Androgens

The androgens studied; DHT, androstenediol, androstenedione, and androstanediol; brought the EL to normal intact levels. DHT(P) at 125 to 1000 ug (12,72,164,177,205) did not differ from their same dosage TP controls, regardless of the treatment regime. No change

over 70 days of injection (205) was indicated. No substantial change occurred with the addition of TP to DHT(P) (12,141,177).

The addition of EB to DHT(P) interfered with the DHT(P) sustained ELs. No statistically significant changes were seen with 0.05 to 50 ug EB (11,144), but a pattern of decrease in the EL with increasing EB dosage did appear. The same decrease was seen when free estradiol (1-5 ug) was combined with DHT (145). On the other hand, estrone with DHT (145) produced larger ELs with the same dosage.

Both androstenediol (AEOL) (46,157) and androstenedione (AEONE) (46,164,205) maintained the EL at intact or TP control values. The AEOL ($\geq$ 800 ug) EL was more variable than that of AEONE. The combination of androstanedione (AAONE) with TP (47) did not cause any change from TP alone, but the combination of AAONE (1 mg) and DHTP (200 ug) did significantly increase the EL (12) over the TP control, but not over DHTP alone.

Adrenalectomy

Adrenalectomy had little effect on the EL, although increases were reported by studies (48,82) of intact and TP castrates. For EB injected castrates, adrenalectomy reportedly (82) increased the EL two fold. Overall, however, due to the limited data, adrenalectomy should be assumed to have no significant effect on the EL.

Drugs

The androgen analogue, fluoxymesterone (FM), maintained normal EL levels to a degree. When compared with TP controls, the castrate FM males, both PNX and sham, produced a gradually increasing EL, at least to 56 days of injection (198). The increase over time did not match a castration (oil control) increase. Furthermore, the FM extended ejaculation and the EL beyond the point of termination for oil controls. In addition, the EL_{1-3} FM effect was reduced with increasing series (198). FM stood intermediate between the same dose of TP and castration alone in its effect on the EL.

Neither of the anti-androgens affected the EL of castrates or those given TP replacement. Cyproterone acetate (10 mg) (49,204) and Flutamide (25 mg) (180) were both ineffective.

Among the anti-estrogens, only MER-25 produced any change in the EL. MER-25 shortened the TP maintained EL significantly ($r = 0.58$) at the 2 mg dosage (47). However, the EL ratio (T+MER/T) then increased to $r = 1.34$ with 28 mg. CI-628 (10 mg) (182), cis-clomiphene (0.25-1.0 mg)(47), and ICI-46474 (0.1-1.0 mg)(47) produced no substantial EL changes of T replaced males.

The aromatase inhibitors were more effective. Both 10 and 22 mg of metopirone reduced the EL, but not to a level of statistical significance (47). AGT reduced the EL to the point of eliminating ejaculation and the EL (47). The effect of a drug on the EL, if any, was always an EL decrease.

Synopsis

The EL was a relatively consistent measure like the PEI. The extremes of the intrinsic variables and testing parameters increased the EL duration. Increases occurred in such variables as age, sexual experience, test time, and time between tests. Manipulations of behavior and sexual and environmental stimuli; such as EICI, EPEI, shock, group testing, and handling; reduced the EL. Conversely, the sensory organ variables (e.g., OBX and PNX) increased the EL.

Castration caused an increasing EL. The addition of TTP and other androgens returned the EL to precastration length. Estrogens gave indications of some retardation of the castration EL. However, estrogen also inhibited the action of androgens, because it effected EL increases in intact males and in combination with DHT. The nonsteroidal androgen, FM, produced an intermediate response, between that of castration and equal TP dosage. Finally, the drugs that were effective; MER-25, AGT, and metopirone; decreased the EL supported by testosterone.

6.5 Ejaculation Frequency

The ejaculation frequency (EF) is the number of ejaculations achieved during a sexual behavior test. Because the length of the test (TMIN) directly limits the possible number of ejaculations, the length is of paramount importance. The relationship of the EF to the TMIN (min.) was linear ($EF = 0.068 \cdot (TMIN)$), until satiety was approached (n = 33 studies). Unfortunately, no data were available

between the 90 minute tests and tests to sexual satiety. The average EF for satiety tests was 6.8 ejaculations; it served as the upper limit of the EF.

No indication of differences due to strain were seen for tests of 90 minutes or less, but strain differences were present with satiety. The Long-Evans (41,56,62,67,74,116,207) and Göteborg (140) males satiety average was EF = 6.80 $\pm$ 0.16, and the Sprague-Dawley (101) and the mixed group (30,77) averaged at EF = 5.90 $\pm$ 0.06.

The relationship of age to the EF was an inverted "U" shape, a hump, with the highest EF values during the adult ages. At the younger ages (<250 days), an exponential increase in EF occurred with increasing age (119,123,140). The decrease in the EF after 560 days of age was more linear (119,124,132,140). The old age decrease was apparently due to a decreasing rate of copulation during a set time, because when given unlimited time to attain satiety, adult EF values were attained.

Testing variables decreased the EF. When males were tested during the light phase, the EF was depressed (r = 0.70) compared to testing during equivalent times during the dark phase (31,119,123). The EF was also decreased by reducing the interval between repeated tests to less than 7 days. The decrease was directly proportional to the shortness of the test interval (30,44,76,119).

Prior sexual experience improved performance over that of inexperienced males. The rate of EF increase due to sexual experience was influenced by the test length (TMIN); as the test duration lengthened, the rate of EF improvement decreased (62,70,127,196). As might be expected, males cohabiting with females prior to testing had a

greatly curtailed sex experience effect (70). However, even with males considered sexually experienced, an effect of repeated testing occurred, athough minor (3,45,50,70,76,101,119,124,127,188,192,198). The increase in the EF disappeared by the third test.

When the condition of rearing or caging was considered, no differences among the three conditions were observed. Neither cohabitation (70,87,184) nor isolation (71,87,184) were different from males raised under segregation conditions. Placing separating screens within the cages, similarly, had no effect on the EF (184).

Behavioral and Stimulus Manipulations

Enforced ICIs resulted in a decreasing EF with increasing EICIs greater than 1.5 minutes (119). The EF decrease followed the same linear pattern, regardless of the number of ICIs experimentally manipulated. Insufficient data (67) were available to establish an EF pattern for EPEIs. Dewsbury and Bolce (67) indicated a decrease due to an EPEI of 60 minutes when males were tested to satiety, but the treatment attained staistical significance in only one of two experiments.

When a new female was introduced at satiety, the EF increased (r = 1.14) (34,56,74,116). However, if the new female was exchanged for the original female at each ejaculation (76,101) or after 90 minutes of testing (45,67), no change in the EF as evident.

Another "excitatory" variable, shock during testing (50,52), elicited an increase in the EF for tests of 60 minutes duration or less (r = 1.35). The rate of shock delivery did not significantly

affect the overall shock increase.

Of the conditioning variables, only the conditioned avoidance to a loud bell provided a significant decrease in the EF (119). Neither of the positive conditioning paradigms, copulation paired to a light or a pedal-pull for access to a female, proved effective (119).

The EF response to environmental stimuli was inconsistent. Reducing the test area by half decreased the EF (50), except when shock was given in addition, at least, for a 15 minute test. Group testing augmented the EF of one hour tests, significantly in one study (119) for both adult and old males and not significantly in another study (120). Testing male-female pairs in adjacent arenas produced EFs intermediate to group testing and the single pair, isolated arena, control EFs. When males were handled during testing, an interaction was found. A significant increase occurred for the EF of old males (20-25 mos.), but not for those of adult age (5-6 mos.) (132).

Sensory Variables

The response of the EF to removal or reduction of sensory input was uniform in direction. When effects occurred, the EF was reduced. OBX (14,45,98,138) and peripherally induced anosmia (138,196) reduced the EF by almost one-half for test durations of 90 min. or less in experienced males. The lack of sexual experience further reduced the EF (196), as did raising the males in isolation prior to anosmia treatment (196). Blinding, however, did not alter the EF (14,89).

Interference with information derived from the penis drastically

reduced the EF. Removal of the penile bone (27) eliminated ejaculation. Severing the dorsal nerves of the penis greatly reduced (r = 0.18) the EF of experienced males (198), but PNX did not eliminate ejaculation. Without doubt, interference with input from the penis was more devastating to the EF than the removal of smell.

Hormonal Variables

Castration induced an exponential decrease in the EF. A zero EF value was reached by 36 to 42 days postcastration when tests were 15 (188) or 20 minutes (198) long. When castrate males were injected with 500 ug or more of TP (20,134,188,198), the EF was comparable to an intact male's, regardless of the injection regime. Although no data were available for lower TP dosages, an exponential approach to the castration EF with decreasing TP dosage was expected.

EB was unable to return the EF from castrate to intact values (20,103,198). However, an indication that the EF may be held above the castrate falloff under maintenance (103) was noticed; but EB may be ineffective under a recovery regime with long-term castrates (20,198). In either case, the data were very scanty, so any conclusions were speculative.

Data for DHT(P) was even more scanty. DHT appeared a poor substitute for testosterone; it did little to return the EF of castrates to normal intact values (198). A noticeable improvement occurred with the addition of EB to DHT (198).

Little data were available for the hormone treatments, because most testing was to the end of the first PEI. For a better description

of hormonal effects upon ejaculation, look to the ratio of males responding (PEPIPM section). The model assumed a castrate EF for all androgens not provided with data.

Drug Variables

The only data provided for the EF for any drug variable was for the androgen analogue, fluoxymesterone (FM). Under a maintenance regime, FM prolonged the EF compared with castrates, but FM was not able to maintain the EF at intact (or TP) levels for very long periods. Where castrate males fell to a zero EF by 42 days post-castration, the FM castrates had an extrapolated zero EF by 86 days of injection (198). The FM essentially doubled the duration of the castrate EF response. When PNX was combined with FM, the drop in the EF was more rapid than castrate controls, but slightly higher than the fall due to PNX castrates (198). However, if at least 50 ug of EB was combined with the FM, the EF stayed approximately at intact levels (103).

Synopsis

The EF was most prone to decreases in response to experimental treatments. When effects did occur; FM, the hormone variables, sensory variables, and the intrinsic variables (age, test time, TBT, and sexual experience) all provided decreases. As a group, the environmental and behavioral stimuli did not produce effects in the same direction. Variables that may be considered "excitatory", such

as a new female at satiety, shock, group testing, or handling of old males, increased the EF over control levels. Only EICIs, negative reinforcement, and reduction of the arena size elicited a decreased EF.

6.6 Mount, Intromission, and Ejaculation Response Ratios (PEPIPM)

The measures utilized most frequently in the study of the sexual behavior of the male rat were measures of the relative numbers of males responding with ejaculation(s), intromission(s), or mount(s) to any given treatment. The most common representation was the percentage of the total number of experimental males exhibiting ejaculation (PE), intromission (PI), or mounts (PM). Otherwise, the number of responding males in one or more of the three sexual events was reported.

The ejaculation measure was the most labile of the three, followed by the more stable intromission measure and the most constant, mount measure. For the purposes of the model and the following discussion, these measures were represented only by their Experimental/Control group ratios derived from the percentage or number of responding males in each of the two groups. For example, if 6 out of a total of 10 castrate males experimentally injected with a low dosage of TP responded with ejaculation and 7 out of the 8 control, intact males responded, the experimental ratio would have been 6/10 = 0.60 and the control ratio would have been 7/8 = 0.875. the model ratio would, therefore, have been E/C = 0.60/0.875 = 0.686.

The model assumed the highest ratio of 1.0 as the baseline for

each of the E, I, and M ratios. The normal male was generally selected for the ability to copulate, i.e., to attain ejaculation, prior to the experimental testing. Therefore, the "normal" male was sexually experienced, intact, of adult age, and rested from prior sexual endeavors. Under these requirements, 100% of the males usually responded, so many studies did not report control values for the response measures; that all respond was frequently assumed. Only when the control male treatments deviated from the above was the reporting of both required, and the E/C ratio became necessary.

Intrinsic and Test Variables

For the most part, variations from the "normal" condition resulted in decreasing E, I, and M ratios (referred henceforth as PE, PI, and PM, respectively). A consistent relationship among the PE, PI, and PM for all variables was always present. The PM was the higher ratio value, closely folowed by or equivalent to the PI, and the lowest ratio was always the PE, simply because mounts were required for intromission and intromissions were required for ejaculation. The PE was, therefore, the most subject to change, making it the most discriminative of the three. Because the PE was the most responsive measure, it will be the most discussed, but the responses of the PI and PM can always be assumed to follow the same patterns of change as the PE but at higher levels.

To establish the relationship of the PE, PI, and PM ratios, studies reporting (179,181) at least two of the ratios for normal males over a number of repeated tests were averaged. Over 5 to 10

repeated tests, the average PI/PE was 1.07, and the average PM/PI was 1.06. These relative factors were used if no other treatment provided differences between the PE, PI and PM.

An altering response to variations in age was noticeable in both young and old males. However, some changes were seen in the adult age group (170-600 days) over the course of a test. As stated before, the experienced adult began at the maximum PE = 1.0 at the first ejaculatory series. With increasing consecutive series, the PE dropped in a sigmoid fashion to approximately PE = 0.52 by the fifth series, the terminus of the model (119,123,127,131,140). The PE closely approached zero by the eighth series. The PI and the PM after the last ejaculation was about 0.55 (140).

A decreasing PE with decreases in the males' age, as puberty was approached, was apparent over all series. The age decreases for each consecutive series were parallel, but at lowering PEs (119,140). A very similar parallel decrease was observed with increasing age (over 600 days). The cessation of ejaculation occurred after fewer and fewer consecutive series with increasing old age (119,123,140).

Testing males during the light phase did not significantly reduce the PE for series one (PE_1)(31,119,123). The Light/Dark ratio for the PI was approximately the same (PI/PE = 1.018)(31). Over the following series, the PE - L/D ratio decreased with increasing series number, and the PE approximated zero by the sixth series (PE_6) (119).

When the time between tests (TBT) was reduced, a reduction of the PE_1 occurred, but only for tests with fixed time intervals and for TBTs of 2 days or less (119). Testing males to sexual satiety

produced no change in PE_{1-5}, but when a 60 minute time limit was imposed, not only decreases with reduced TBTs occurred, but also decreases with increasing series was evident (119). Bermant et al. (44) demonstrated no effect of low TBT (1.5 - 24 hours) after a 90 minute test. No like data for PI or PM were available.

The effects of sexual experience interacted with age, which was not always controlled for. No substantive changes in the PE occurred for males less than 260 days of age (119,127) that could not be accounted for by age effects. Drori and Folman (70) reported substantially lower PEs in inexperienced males over 470 days old, but they tested for a little over 15 minutes. Because the Drori and Folman data did not agree with the others, the effects in the model were limited to older males receiving shorter tests (TMIN $\leq$ 20 min.). This study (70) did provide relative information on the PI. The PI ratios (Inexp/Exp) started higher at the first test and rose faster than the PE (on the average, PI = PE + 0.40).

The caging condition resulted in a divergence in response among the strains. When the isolate condition was compared with the segregate, a gradual increase in the PE occurred over repeated tests. However, the Sprague-Dawleys (80,105)(PE_{min} = 0.011) began at a lower PE than the other strains (22,87,206)(PE_{min} = 0.026). Under the cohabitation condition, the same strain split was evident. No difference was seen between the cohabitant and the segregate Sprague-Dawley males (80), but a decrease in the PE from a ratio of 1.58 occurred for the remaining strains (70,87). When a screen was placed between two males or a male and female, the PE was equivalent to males raised in isolation (80).

The PI of the isolation condition was either equivalent to (87,206) or greater than (86,105) the PE ratio (PI/PE = 1.30). For the cohabitation condition, no change occurred between the PI and the PE (70,87,105,206). The change from PI to PM was slight for the isolation condition (86,87,105,206), producing an average PM/PI of 1.09. Again, no PM-PI change occurred for the cohabitation condition (87,206).

Manipulations of Behavior and Stimuli

The enforcement of ICIs produced decreases in the PE for one EICI in an ejaculatory series (119). The E/C PE ratio decreased with intervals greater than 3 minutes, and the PE ratio decreases were augmented by increasing series. For example, a 7 minute EICI resulted in a PE_1 = 0.72, but fell to zero by PE_4 (119). No data were available for EPEIs.

When a new female was substituted for the original test female at satiety, a small but consistent increase in the PE (r = 1.30) (56,101,207) occurred. With a fresh female at satiety and at each ejaculation the PE increase was larger (r = 2.25)(101). The PI (101,207) and the PM (101) effects were larger than for the PE. Bermant et al. (44) provided data demonstrating no TBT effects after the introduction of a fresh female following a 90 minute test; a potential PE drop occurred only on the third series of the following test for TBTs of 3 to 18 hours.

The stimulation of shocks during testing did not affect the PE of sexually experienced males (23,81,174), but the PE of inexperienced

males (50,81) was improved. Shock given to castrate males inhibited the falloff in PE postcastration (9). In addition, shock given to very young males ($\geq$ 45 days) caused males to respond at a younger age with ejaculation (81).

Shocks during testing for the PI and PM were affected approximately the same as the PE for experienced and inexperienced males (9,23,50,51,174). The relative increase in PI for castrated males was comparable to that for the PE, but the PM demonstrated a greater increase. Shock maintained a nonzero PM beyond that for the non-shock controls over the days postcastration (9).

When shock was given at higher levels, more painful levels, males stopped ejaculating (23). With high shock, the PI fell over a few repeated tests to a zero level, but the PM decrease was more gradual. The PM ratio was initially at a complete response level (PM $\cong$ 1.0).

Electroconvulsive shock induced an increase in the PE, approximately double the non-shock control level (23,26). The rise held over several tests. No significant increase due to ECS occurred in the PI or the PM (26).

Shock was also used as a conditioning stimulus. Starting at 38 days of age, males were shocked for approaching a female and tested as adults for sexual behavior, either in the shock apparatus or in a novel arena (208). The shock training produced a statistically nonsignificant decrease in the PE and PI when tested in the shock apparatus. In the novel arena, those decreases were eliminated. However, males conditioned to pull a pedal for access to a female demonstrated no change in PE_{1-5} (119) over the untreated controls.

An alternate change of the test environment was the reduction of the test cage by one-half. The half cage produced a large decrease in the PE ($r = 0.21$), but the overall decrease was small when shock during testing was added ($r = 0.765$)(50). No effect occurred with the PI or PM.

Males tested in groups of males and females showed a PE improvement (119). Adult males had a gradual increase in the PE ratio with increasing series number, and the rise in PE for old males (25 mos.) was greater with later series, when compared to a single pair tested alone. Male-female pairs tested in adjacent arenas had PE increases less than the group males, but slightly better than those tested alone. A similar intermediate response level existed for the old males in adjacent arenas (119).

A variety of sexual stimuli produced decreases in the PE, PI and PM. Early exposure (Day 37 on) to receptive female or male stimulus objects produced a decrease in the PE of later tests, but no substantial change in the PI or PM occurred (105). When males were actually treated to stimulus objects other than a receptive female as adults, all responses were greatly reduced. A nonreceptive or immobile receptive female, a male, or a guinea pig, sexual stimulus resulted in zero PEs and PIs for inexperienced, isolate males (13,14,17). Regarding the PM, the nonreceptive female was the more effective stimulus ($r = 0.575$) with the immobile female, male, and guinea pig a weak second ($r = 0.20$), compared with a receptive female stimulus. When these males received high doses of TP, their PI and PM ratios improved (14,17). Similarly, when a vaginally closed female was the sexual stimulus (200), the PE was zero, but no effective changes were

reported for the PI or PM.

The PE, PI, or PM measures did respond to most of the manipulations of behavior, testing environment, and sexual stimuli. The manipulations considered "excitatory" increased at least the PE. These manipulations included: a new female at satiety, shock, ECS, and group testing. The treatments of EICIs, high, painful shock levels, avoidance conditioning and alternate sexual stimulus objects appeared to either interfere with ongoing behavior, or provided insufficient stimulation.

Sensory Variables

The sensory variables uniformly reduced the PE, and often the PI and PM as well. OBX, blinding, facial (5^{th}) nerve cuts, and reduction of penile innervation were effective manipulations.

Olfactory bulbectomy (OBX) produced a minor PE decrease ($r = 0.80$), regardless of the sexual experience in all but one strain (14, 45,98,100,168). The PE of OBX Wistar males was far lower ($r = 0.28$) (137,138,139,206). All Wistar experiments took place in Larsson's laboratory, so the differences may be due to strain. The OBX PI ratio averaged up to double that of the PE ratio, but the PI responses were highly variable (14,45,98,137,138,139,168,206) with no strain differences. The PM was only slightly higher than the OBX PI (14,45,137,138,139,206). Peripherally induced anosmia did not differ from the OBX treatment (138).

Males raised in isolation had OBX/sham PE ratios further reduced from the "normal" males raised as segregates (139,206). However,

those males raised in cohabitation had higher OBX PE ratios (139,206) by a factor of three. The PI was higher than the PE in OBX, isolate and sham males, but the cohabitants demonstrated little change from PI to PE (139,206). The change in PM due to OBX was not different among the raising conditions. The interactions of raising condition with OBX were based solely on Wistar data.

No significant differences were reported for OBX males given 250 ug TP or 10 IU FSH + 3 IU LH/kg BW (137). Neither hormone treatment compensated noticeably for the effects of OBX.

Blinding produced a wide range of results. The PM effects ranged from no change from sham males (185) to an intermediate PM decrease (84,85) to low levels of response (13). The average PM E/C ratio was r = 0.62. The data for the PI and PE response to blinding was scant (13). The PI was equivalent to the PM, with the PE 20% lower.

All penile treatments produced a decrement in the PE and the PI. The reported treatments included removal of the glans penis or the penile bone, anesthesia of the penis, and severing the Pudendal or Dorsal Penile nerves. Removal of the penile bone prevented ejaculation, resulting in a zero PE, and the PI was severely reduced (27). The PM was unaffected. On the other hand, no change was indicated with the removal of the glans (183).

Penile anesthesia, produced with topically applied Lidocain, did reduce the PE_1 by one-half (1,142), and further reduced the PE_2 (1). A limited effect was produced on the PI_1, and a large decrease occurred in the PI_2 (1). The PM was unaffected.

Sectioning any of the nerves innervating the penile area

depressed the PE by almost two-thirds in experienced males (118,150, 198), and the PE decreased further with increasing series (198). The PNX PI was approximately 2.5 times greater than the PE (118,198). The PNX PM was not different from controls (118,149,198).

The PNX responses of males raised in isolation or given no prior copulatory experience were even further reduced. Isolation (118) reduced the PNX PE almost to zero. The PI reduction was about one-third, but the PM reduction was negligible. The only comparative data on sexual experience and PNX was for the PM (149). The PM was reduced by almost one-third if no sexual experience was given prior to PNX. Males given experience just after PNX did not differ from males given no experience.

When PNX males were castrated and injected with DHT(P), the PEs were further reduced, but the PIs were reduced only with extended treatment (198). Beyond the first series, the PI and PM were also reduced. The addition of EB eliminated the interactive reductions (198).

Other treatments affected the males' response. Sectioning the facial nerves (13) eliminated the PE and reduced the PI and PM by half. Bursts of loud sound doubled the PI (51), no doubt having some "arousal" effect like shock; unfortunately, this was the closest approach to the sense of hearing. Furthermore, when more than one of the senses were removed, all three measures dropped to zero (13); the males did not respond.

Hormone Variables

Castration resulted in an exponential decrease in all three measures of responding males. All measures approached zero by 70 to 80 days postcastration. No difference in the dropoff in the PE postcastration was found among the Long-Evans (48,49,58,148), Sprague-Dawley (103,160,205), Wistar (28,160,163,181), Göteborg (134) or mixed (32) strains. The dropoff was somewhat more rapid in the PE than the PI (28,103,134,181,186,198,205), and the PI than the PM (103,134,181,198,205). The postcastration decreases were further augmented with increasing series (58).

Testosterone

The PE, PI, and PM data for testosterone treatment in castrate males were the best available for any behavioral measure. Sufficient data were provided to separate the data into recovery or maintenance regime categories. The regime data were subdivided into free T or TP studies and sexually experienced versus inexperienced male groupings.

The first category was inexperienced males given free T under recovery conditions. The PE, PI, and PM were affected by both dosage and days of treatment. Under recovery, male responses started at zero and followed an exponential increase to approximately 1.0 with extended days of injection of 300 to 1000 ug T (46,47,141,151,157,164). The rate of increase over days of daily injection was dependent on the dose. The return of the PM to intact levels began with fewer days of injection than the PI; the PE return began even later.

The same pattern of response return occurred with the inexperienced males given 45 to 1000 ug of TP (47,133,135,136,144,145,177). As with T, the rate of increase was dependent on the dosage, but the rate was slightly greater with TP. The responses were initiated in the same PM, PI, PE recovery order, but in all cases, the TP injected males began responding earlier than the T males, on the average.

When recovery males were sexually experienced, the response to TP was substantially enhanced over the inexperienced males. From 100 to 500 ug TP (12,27,49,72,82,176,180,181), the rates of increase were larger and the initiation of response was earlier. In most cases, the males were responding with ejaculation after the first day of injection.

The age of castration influenced the later adult response to TP. When males were castrated before 13 days of age, the recovery of the PE (133,135) was retarded. The PE retardation increased with earlier ages of castration. With castration at the age of 3 days, ejaculation did not appear (135), and the PI and PM were severely depressed.

Under a maintenance regime - using sexually experienced males in all reported cases - low doses of TP held the PE, PI, and PM at normal intact levels. A falloff in the PE occurred only with less than 25 ug TP (32,49). The falloff was more rapid with lowering dosage, until the castration falloff was approximated. Doses of 25 ug to 800 ug (28,32,159,160,198,205) showed no consistent change in the PE over 70 days of injection. The same lack of change occurred with 25 ug or more for the PI (28,198,205) and PM (82,198,205), but no data were available for the PI or PM at lower dosages.

Testosterone was delivered in a more continuous manner than daily injections through the implantation of silastic tubing

containing crystalline or concentrated T solution. A 5 or 15 mm long T implant maintained the PE, PI, and the PM at intact levels when the implant was inserted at castration (178). The 15 mm implant restored intact levels in males castrated 40 days prior, but no comparative data for shorter implant lengths or TTP injections were available (205).

Damassa et al. (57) provided an indication of a dose response in T implanted males on a long-term maintenance regime for the PE. A slight decrease was seen with a 5 mm T implant ($r = 0.85$) and a greater decrease at the 2 mm size ($r = 0.74$).

Implants of T were also capable of reducing the age for the onset of response (205). Intact males implanted at 14 Days of age displayed ejaculation 12 days earlier (at 31 Days old) than oil implant controls. Similar early responding occurred for the PI and PM, occurring earlier and with higher levels than the PE. The rate of change after onset was approximately the same in the implanted and control males.

Testosterone was bonded to different chemical additive that altered the time the testosterone remained in the rat's body. To test their longevity, the testosterone forms were injected in a single, large dosage (10 mg). Under maintenance conditions, testosterone phenylacetate (TA) had comparable PEs to TP, but the PI was prolonged almost twice the time for TP (33). With a recovery regime, the TA males responded with ejaculation twice as long as with TP (35). Both testosterone cypionate (TC) and testosterone enanthate (TE) lasted three times as long as TP (35).

Demonstrable effects were seen with testosterone on the PE, PI,

and PM. The PE was the more labile, decreasing earlier with low TTP doses and reaching a zero response before the PI. Similarly, under recovery, the PE was the last to appear and the last to attain intact response levels. In the same way, the PI as more subject to change than the PM. These patterns held regardless of the reductions due to the lack of sexual experience, the age of treatment initiation, the method of testosterone delivery, or the chemical form of the testosterone.

Estrogens

The categories followed for testosterone were followed for the estrogens, principally estradiol (E_2 or EB forms). The responses to estrogen were compared with intact males or TTP (100 ug or more) treated castrate controls. Data were available for recovery and maintenance regimes, experienced and inexperienced males, injection and implant delivery, and combinations of EB with testosterone.

The recovery treatments with EB injection produced little (60,143,164,176,177,198) or no increase (141,144,152,177) above a zero PE. Zero PEs occurred with 5 ug or less and the small increases occurred with 1 to 200 ug EB with no reliable dose response. The PI from the same studies (60,141,144,152,164,177,198) started to increase above zero earlier than occurred for the PE, and attained response levels twice those of the PE. The PM (144,152,164,176, 177,198) was only slightly more affected than the PI.

Experienced males proved substantially more responsive to EB than inexperienced males, at least, at high EB (100 ug) dosages

(176). The majority of experienced males responded with ejaculation by 16 days of injection, by 8 days for PI, and by 2 days for PM. The recovery increase was less than for the same dosage of TP (176).

No comparative data were available contrasting the two estrogen forms, free and benzoate, but some information (145) was available comparing the different estrogens: E_1, E_2, and E_3. The PE and PI did not rise above zero under recovery in inexperienced males with the three estrogens (1 & 5 ug). Estradiol (E_2) was two to three times more effective in increasing the PM as either estrone (E_1) or estriol (E_3).

Injection of EB at castration into experienced males (59,82,103) was incapable of maintaining the PE at intact levels with dosages of 50 to 100 ug EB. On the other hand, the PEs were greater than for the castrate controls. The PI had some decrease from intact values, but the PM remained at the intact level (82,103).

Furthermore, the delivery of estradiol by silastic implant to young intact males (14 days of age) did not significantly alter the development of the early PE and PI (178). The effect on the PM was comparable to T implants.

The combination of EB (1 ug) with TP (200 ug) produced a greater PE, PI, and PM than TP alone under recovery conditions (177). Therefore, EB augmented TP rather than interfered with response to TP.

Overall, estradiol, particularly the EB form, produced greater improvement in the number of males responding when they were experienced. The response did not approach that for TTP, however. In many studies of inexperienced males, the PE did not rise above

zero. The responses did increase over time under recovery regimes, but the variability among studies made a definite dose response curve difficult to establish. Under maintenance conditions, EB was not capable of maintaining intact levels, but the response levels did not fall to castration values. Although free estradiol and its EB form were not compared, some evidence was provided showing E_2 more effective than E_1 or E_3. Furthermore, EB augmented the effects of TP. The responses to estradiol may best be characterized as intermediate to intact or TP and the untreated castrate condition.

Dihydrotestosterone

Dihydrotestosterone (DHT) was utilized in both its free and propionate forms. Sufficient data were available to segregate recovery and maintenance regimes, but they were insufficient to separate effects due to sexual experience. DHT(P) was frequently combined with estrogen (usually EB), and sometimes with testosterone.

No consistent differences among the reported dosages of 125 to 1000 ug of DHT(P) under recovery conditions were observed. Furthermore, no differences could be established between sexually inexperienced (12,143,144,145,152,164,177) and experienced (72,198) males. The PE rose gradually, in most cases, to an average PE of 0.20 after 24 to 60 days of daily injection. The PI was only slightly higher, and the PM a touch above the PI.

Dosages of 150 to 1000 ug of DHT(P) did not maintain the PE at intact levels immediately following castration in sexually experienced

males (159,160,163,198,204). The PE dropped to the r = 0.20 level by 42 days of injection. The PI did not start to drop until two weeks following the PE falloff, but the rate of descent was the same (198,204). The PM started to decrease at the same time as the PI, but the rate of decrease was half that of the PI (198,204).

The combination of DHT (500 & 1000 ug) with TP (200 & 1000 ug) increased the PE, PI, and PM over the values for TP or DHT alone (141,145,177). Under a recovery regime, the DHT + TP increases began earlier than those of TP, and the rate of increase was doubled.

The combination of EB (.05-50 ug) with DHT (1000 ug) was also a very effective treatment. The increase in the PE for inexperienced males under recovery conditions was far greater for EB + DHT than for DHT alone (143,144,152,198) and equal to and sometimes greater than a 1 mg TP control (127). The same relationships held with the PI and PM (143,144,152,198).

When E_2 (1 & 5 ug), E_1 (1 & 5 ug), or E_3 (1, 5, & 25 ug) were used in place of EB in combination with DHT (500 ug), the responses were similar to the EB combination with some variation. The recovery PE with E_2 + DHT was greater than DHT alone, and showed a greater increase than even the TP (200 ug) control (145). At the same dosages, the E_1 proved less effective in inducing total recovery than E_2, and E_3 was less effective than E_1 (145). No statistical comparisons were made between the three estrogens. The TP control PE was closest to that for E_3 + DHT. Again, the PI and the PM followed the same relative relationships (145).

In general, DHT injections had relatively weak effects on the ratio of males responding with E, I, or M. The recovery with DHT was

slow and never attained intact levels, and the DHT was not able to maintain maximal responding over extended treatment. However, synergism occured when DHT was combined with estrogen. The relative effectiveness of the different estrogens followed the decreasing order: estradiol, estrone, and estriol. The combination of DHT with TP produced responses greater than TP alone, but not significantly.

Other Androgens

Data were available for most of the minor androgens under both the recovery (inexperienced males) and maintenance (experienced males) regimes. The relative effectiveness of these androgens was assessed by comparison with the same dosage of T or castrate controls.

For the recovery treatments, the PM was the best comparator among the androgens. The PM for both androstenediol (AEOL)(46,157) and androstenedione (AEONE)(46,157,164) approached that of T, with large variation among the studies. In one case (46), AEONE was equivalent to T and greater than AEOL (1 mg); in another, AEOL was equivalent to T and greater than AEONE (1 & 3 mg)(157). The PI and PE were similar between AEONE and AEOL, and these were somewhat less than the T control.

The remaining androgens produced very little increase above castrate levels at a 1 mg dose (46). 11β-hydroxy-androstenedione and dehepi-androsterone were somewhat more effective than 3α- and 3β-androstanediol, androstanedione, and androsterone. The latter group produced a zero PI, and all the above had a zero PE.

Maintenance treatments had a similar relative effectiveness.

AEONE proved effective in maintaining responses at T control levels over 70 days of injection at a 800 ug dose (205). However, at 150 ug, AEONE was only slightly better than the oil castrate (160). 19-Hydroxytestosterone (HTP)(159) and androstanedione (160) demonstrated some ability to retard the postcastration falloff of the PE. However, androsterone, both isomers of androstanediol, and hydroxyandrostenedione approximated castrate PEs (160).

A few cases of a combination of androgens were found. When 1 mg of 3β-androstanediol was combined with 200 ug DHTP, the combination was significantly more effective than DHTP alone in inducing PE recovery (12), but not as effective as 200 ug of TP. The combinations of HTP (100 ug) with DHTP (100 ug) and estradiol dipropionate (100 ug) with DHTP were both capable of maintaining the PE near intact levels, but were not significantly greater than a 200 ug dose of DHTP (163).

The relative effectiveness of the androgens compared with testosterone followed a similar order under both treatment regimes. The PE was the primary response measure. Testosterone was the most effective, closely followed by AEOL and AEONE. The second grouping, showing a lesser effect, included HTP and dehepiandrosterone. An intermediate group included: androstanedione, hydroxyandrostenedione, and DHT. The last and most ineffective group was composed of the two isomers of androstanediol and androsterone. This ordering was far from conclusive as only one or two studies provided the relative responses. The data on AEOL and AEONE demonstrated the variability in relative positioning.

Adrenalectomy

Adrenalectomy did not alter any of the responses to testosterone injection of castrate males. Neither recovery (48) nor maintenance (48,82) schedules provided any significant changes in the PE. However, adrenalectomy did substantially reduce the maintenance effect of EB (100-150 ug) for the PE, rapidly pushing the PE to almost zero. The EB control responded at near normal levels. No significant effects occurred for the PI or PM (82). Furthermore, no changes in intact or castrate males (48) were observed due to adrenalectomy.

Drug Variables

All the drug treatments contained within the model were represented by PE, PI, and PM data. The nonsteroidal androgen, FM, the anti-androgens, anti-estrogens, and aromatase inhibitor groups were all represented. The effectiveness of the drugs was assessed by comparison with the nondrug controls, that were usually TTP injected castrates. Most drugs were expected to decrease the effect of the TTP treatment.

The FM data was reported for a maintenance regime only. The FM PE over 56 days of injection was very similar to the same dose of TP (500 ug); only a very small PE decrease occurred toward the end of treatment with FM (198). The minor difference was even less pronounced for the PI and PM. The drop in effectiveness of the FM compared with TP became more pronounced in series 2 and 3 (198).

Furthermore, FM (400 ug) significantly affected the injection of EB (50 ug). The FM when combined with EB maintained the intact PE. The differences between the FM + EB and EB alone were less pronounced for the PI, and both groups performed at normal PM levels (103).

The first anti-androgen under consideration, cyproterone acetate (CYA), had recovery and maintenance data. CYA (10 mg) had no effect on castrate males or on DHT treatment under a recovery regime. However, CYA did improve the effect of EB (1 ug) for the PI and PM, and CYA interfered with the recovery rise due to the EB + DHT for the PI and PM (152). The PE did not rise above zero for any recovery treatment (152). On the other hand, CYA did not interfere with the PE recovery rise due to TP (100 ug)(49). Furthermore, CYA was capable of maintaining PEs longer than the non-CYA castrates, and the androgen effects of CYA alone were similar to those produced by 8 ug TP (49).

The anti-androgen, Flutamide (FL)(25 mg), substantially inhibited the TP (100 ug) PE recovery rise. The inhibition of the PI was less noticeable, and the effect was not apparent with the PM (180). No androgen effects of FL were indicated when FL was given to castrates or intact males (180). The anti-androgen, SH-714 (3 mg), produced a decrease in the PE of intact males (209).

The first anti-estrogen under consideration, MER-25, produced ambiguous results. The recovery with TP (800-1000 ug) was not altered by MER (20 mg) for the PE, PI or PM (47,151). However, MER (10 mg) did increase the recovery rise due to DHTP (200 ug)(12). MER had no effect on castrate males (151).

The anti-estrogen, CI-628, did significantly reduce the PE recovery with 800 ug T (151). The CI injections (2.5-4.0 mg) depressed

the rate or recovery increase by approximately half for the PE, PI, and PM. When given alone to castrates, it did not induce any recovery.

Another anti-estrogen, cis-clomiphene (CLOM)(0.25 & 1.0 mg), did not significantly alter the recovery PE, PI or PM with 1 mg T (47). On the other hand, high dosages of ICI-46474 did reduce the recovery to the 1 mg T (47). The PE was not significantly depressed for the 40 and 130 ug ICI doses, but statistical significance was seen for the 400 ug dose. The same depression pattern existed for the PI and PM. In fact, the PE was kept at the zero level over 20 days of treatment.

The degree of success in depressing recovery with TP by the aromatase inhibitors was similar to that for the anti-androgens and anti-estrogens (47). However, the TP treatment for these drugs was an uncommon one; TP was given in a single injection of 6 mg. Neither Metopirone (20-45 mg) nor androstanedione (5-10 mg) were effective. Aminoglutethimide (AGT) was extremely effective at 10 and 30 mg doses. AGT prevented any rise in the PE and PI, and except for one male, the PM. However, the manner of TP delivery as a single injection raised some doubt as to whether as large an effect would have been produced with repeated TTP injection of lower dosage, as utilized by the other drug studies.

The inhibiting effects of the drugs interfering with testosterone or estrogen action were not strictly confined to any particular category of drug. Two-thirds of the anti-androgens, FL and SH; one-half of the anti-estrogens, CI and ICI; and one-third of the aromatase inhibitors, AGT, effectively reduced the recovery increases due to testosterone injection. The AGT appeared the most

effective. The synthetic androgen, FM, did maintain responses to a large degree, but not to the full extent of the same dosage of TP.

Synopsis

The PE proved the most responsive to all experimental treatments. It was potentially the best indicator of changes over time, particularly for the hormonal treatments, when sufficient numbers of males were involved. For the purposes of effective modelling, males from two or more studies were necessary, amounting to 15 to 20 males. For the establishment of clear patterns, at least three studies were considered best.

The PE, and usually the PI and PM, was affected by intrinsic, behavioral, stimulus, sensory, hormonal, and drug variables. The effects of the sensory variables - OBX, blinding, or PNX - were the the most consistent of all variable classes; they produced only decreases. Age extremes, day testing, short TBTs, and isolation produced decreases. Those variables considered "arousal" or "excitatory" stimuli produced increases in response; these variables included: a fresh female at satiety, shock, ECS, and group testing. Treatments such as the EICI, high shock, avoidance conditioning, halfcages, and sexual stimulus objects that were not receptive females all produced decreases.

The hormone variables demonstrated varying degrees of response. Testosterone injections effected normal intact levels of response at dosages greater than 25 ug. Similar effects occurred with T implants. Estradiol induced some improvement over control castrate

levels, but not near those of TTP. E_1 and E_3 were less effective than E_2 or EB. DHT(P) proved to be a relatively weak androgen with these measures, producing only small recovery increases and not maintaining responses over extended periods. Androstenediol and androstenedione were the most effective minor androgens, and hydroxytestosterone and dehepiandrosterone were more effective than DHT(P). The deficits with DHT(P) were eliminated when EB was added to the picture. At least some of the anti-androgens, anti-estrogens, and aromatase inhibitors were effective in inhibiting the recovery rise of TTP castrates. The nonsteroidal androgen, FM, was partially effective. Adrenalectomy provoked changes only when combined with EB. Overall, the number of males responding, particularly with the PE, served as a highly effective measure, showing the decay of behavior in a gradual manner, easily observed, rather than the very terminal changes in the other sexual behavior measures such as the IF and PEI.

6.7 Penile Papillae and Weights

The penile measures are primarily indicators of the androgenic potency of a variety of hormones on peripheral structures. The model provides information on the condition of the penis because the condition of the penis and the resultant sensory input to the CNS is important to the intromission and consequent ejaculation. The number of cornified penile papillae are counted on a cross-section of the glans penis. The papillae appear as convolutions of the surface of the penis, and they increase the penile sensitivity to stimulation.

The penis weight refers to the wet weight of the whole penis, although the glans and the shaft are sometimes weighted separately. The diameter and length of the penis are other reported measures, but they had insufficient data support for comparison.

The papillae measure was the most sensitive to changes in the adult rat, as it varied from zero to a maximum; the penis weight had a substantial inherent mass and structure prior to any androgenic increments or decrements. The papillae and weight measures were combined in this summary, because they responded similarly.

The average number of penile papillae (PP) or spines in normal control males - i.e., intact, naive males - was 65.5 $\pm$ 3.3 ($\bar{X}$ $\pm$ SE, n = 12 studies) for all strains but the Long-Evans. The Long-Evans average was 87.3 $\pm$ 13.3 (n = 5 studies). The range in PP number was 47 to 83, with the Long-Evans extending the range out to 109. The penis weights (PW) ranged from 66 to 121 grams/100 g BW or 222 to 481 g whole weight with an average of 93.0 $\pm$ 5.4 g/100 g BW (n = 8) or 326 $\pm$ 20 g whole weight (n = 10). The weight of the glans was close to 1/3 that of the whole penis.

Behavioral Influences

Copulatory experience increased penis weights. Cohabitation with cycling females (69,75,99,194) prior to testing as adults produced significantly higher penis weights than segregation with males or isolation. No differences in the number of penile papillae (PP) or penis weight (PW)(195) was found between isolation and segregation.

The same increase was evident with repeated mating experience as adults. Sexual tests to at least one ejaculation twice a week increased PWs (75,194), but ejaculation once a week (75) or intromissions only (194) was ineffective. The PP were unchanged by intromissions only, physical stimulation of the penis, or handling (195). An effect of regular sexual experience on the PP was not established; the only related data demonstrated no difference between the PP of males that were maters and those that were non-maters (195). Furthermore, the number of PP were unaffected by section of the Pelvic or Pudendal nerves (150), indicating the maintenance of the papillae was not neurally determined.

Castration

The data showing the reduction of the penis following castration were extremely limited. The PP decreased to 5% of normal intact numbers by 21 days postcastration (32). The drop was exponential starting 6 days postcastration. No data provided a falloff pattern for the PW, but the minimal weight after prolonged castration was approximately 27% of the intact weight (111,112,113).

Testosterone

Testosterone data were available for a variety of treatments. With multiple injections, discriminations were possible between maintenance or recovery regimes and between free T and TP. The time course following a single injection of TP or TA was presented also.

Under maintenance conditions, the number of papillae were sustained at intact numbers by 75 ug of TP (32). With lower dosages, the decrease was dependent on both dosage and the length of treatment (32,49). For example, a 5 ug dose produced 70% of normal numbers with one week of injection, but by 28 days of injection the amount had dropped to 33% of normal.

The recovery data for the PP were too limited to establish a dose response. A single study (177) reported normal PP numbers with 50 to 1000 ug TP. The model recovery dose response was established from the minimal values from the maintenance studies. Following a single injection of 10 mg TP, the PP rose to a maximum by 7 days after injection, remained high for two weeks, and dropped to a minimum in another week (33). A single injection of 10 mg TA (phenylacetate form) proved more effective than TP (33). PP number rose to normal numbers by 2 weeks postinjection, remained maximal for 3 weeks afterward, and dropped to about one-half normal after two more weeks.

The effects on penis weight were available for recovery conditions. Normal intact weights were attained with between 200 and 500 ug of TP (113,177). On the other hand, more than 1000 ug of T was required to attain normal weights, and the degree of effect was related to the number of repeated days of injection (111,113). Comparison of the two forms of testosterone showed T 70% as effective as TP, considering both dosage and treatment time.

Estrogens

The information on the various estrogens was insufficient for totally reliable predictions of changes due to dosage or days of injection, but some estimations were made. Free estradiol (E_2) and estrone (E_1)(1-5 ug) produced a significant increase in PW in long-term castrates (145). E_1 and E_2 tended to be slightly more effective than estriol (E_3), but none of the increases from the castrate level were large (r = 1.45 to 2.0). On the other hand, E_3 at high dosage (60-180 IU) did tend to reduce the PW of intact males (106). In castrates, the higher dosages of E_3 showed no effect on the PW (106).

The two penile measures were not in agreement for the estrogen treatment. EB (1 ug) produced PWs near those of 200 ug TP after 20 days of recovery injections (181). The same EB treatment was substantially less than for the TP control for the PP (181). Furthermore, combination of high E_2 with low TTP dosages produced no significant change, but reduced the effect of TTP on the PW (110,111) and the PP (177).

Therefore, the three estrogens increased the PW over castrate weights, with E_3 the lesser in effect. The increases, however, were minimal (approximately 35% of 200 ug TP response). EB was noticeably more effective on PWs than any of the free forms, but relatively ineffective on the PP. Combination of E_2 with TP reduced the effect of the TP. As the dosage of E and TP were similar and the weights were halfway between the independent T and E effects, the two hormones were probably interacting competitively.

Androgen Influences

A variety of androgens, other than testosterone, had effects on penis weight and papillae number. Both recovery and maintenance regimes were represented, although recovery was preeminent. The androgens will be described in order of effectiveness.

DHT(P) could not be distinguished from TP of the same dosage. The equivalence held for maintenance (159,160) and recovery (12,72, 73,164,177) with 125 to 1000 ug dosages for the PP, and also held for PW recovery (145,164,177).

Similarly, combinations of EB or TP with DHT(P) were equivalent to TP or DHT(P) alone. Recovery was the only reported regime. EB doses ranging from 0.5 to 167 ug combined with 125 to 1000 ug DHT(P) had PP numbers equivalent to TP (4-200 ug) or DHT(P) controls (11,73, 144). Control PWs were found with 500 ug DHT combined with E_1, E_2 (1 & 5 ug), or E_3 (1-25 ug) (145). As might be expected, combinations of TP (4-200 ug) and DHT(P) effected no substantial change from DHT(P) alone on the PP (11,73,177) or PW (94,145,177). The same lack of change held for DHTP with 3β-androstanediol (12).

The effect on the PP of the remaining androgens was similar in a few cases. Androsterone (160,164) produced better than one-half the intact papillae number with 150 ug (160), and was equivalent to the intact at 1000 ug (164). At 150 ug, 3α-androstanediol, androstenedione, and androstanedione (160) were very similar to androsterone under 35 days maintanance. 3β-androstanediol (160) was less effective than its isomer, and 19-hydroxyandrostenedione (160) and 19-hydroxytestosterone (HTP)(159) were totally ineffective. HTP was ineffective

even at 1800 ug.

The androgen effects on penis weights were assessed under recovery and maintanance conditions. The data dealt with androstenedione (AEONE) and androsterone (AND). AND was on occasion altered to a diol form and both forms were normally fat soluble or altered via estherization to a water soluble form. In some cases, a distinction could be made between dose responses under recovery and maintenance.

In general, the order of effectiveness followed: AEONE, AND-diol, AEOL (androstenediol), and AND. AEONE (112) and AND-diol (108, 114,115) were similar under recovery with an oil vehicle. Both approached intact PWs in the 700 ug dosage range. AEOL (110,112) was intermediate. AND (107,114,115,164) effects were the smallest, and its effectiveness was highly variable. According to calculated model relations, the dosage required to produce PWs midway between those of castrate and intact males at 20 days with injection were respectively: AEONE (midpt = 155 ug), AND-diol (mp = 51 ug), AEOL (mp = 590 ug), and AND (mp = 1132 ug).

A maintenance regime required a lesser dosage to attain the same effect with 20 or more days of injection. The midpoint dosages under maintenance were mp = 31 ug for AND-diol (115) and mp = 603 ug for AND (115) in oil solution. The maintenance/recovery ratios were respectively; r = 0.61 & 0.53.

The water solutions proved less effective than the fat (oil) solutions at the same dosage. The midpoint dosages calculated for the androgens were mp = 520 ug for AND-diol and mp = 1100 ug for AND under recovery conditions (114,115). Therefore, the relative effectiveness of the water solution, expressed as the inverse of the

water/fat ratio, were r = 0.10 & 0.54, respectively.

Therefore, the relative ineffectiveness (PW) of androsterone was established compared to that of androstenedione and androstenediol. The addition of hydroxyl groups to produce androsterone-diol greatly improved the effectiveness of androsterone. A maintenance regime required less androgen than recovery to produce equal effects. Finally, the water soluble forms of androsterone were at least one-half as effective as in oil solutions.

Drugs

Data were provided for the androgen analogue, fluoxymesterone (FM), the anti-androgens - cyproterone acetate (CYA) and flutamide (FL) - , and the anti-estrogens - MER-25 and CI-628. The only effects were produced by FM, CYA and FL.

FM at 500 ug was able to bring castrate papillae numbers up to intact levels (36). CYA demonstrated some androgen properties by maintaining castrate (49,152) and EB (1 ug) castrate males at PP numbers midway between the intact and castrate males. However, CYA (10 mg) reduced the PP by one-half in males given TP replacement (49), but it had no effect on intact males (37). CYA only slightly reduced the PP maintained by DHT (1 mg), and was ineffective with EB plus DHT (152). PWs were not altered by CYA in castrate or EB treated males, but some depression of the DHT and DHT + EB highs was observed (152). However, FL (25 mg) did decrease TP sustained papillae and PWs, but it did not affect castrate males (180).

The remaining drugs combined with T or TP did not alter the

testosterone maintenance of the penis. The number of PP were unaffected by 10 mg MER-25 (12). Neither MER or CI affected the PWs of castrates alone or with T (151).

Synopsis

The penis measures, the number of epidermal papillae (spines) or penis weight, usually agreed in response, but the papillae number was more sensitive to most variables. Several behavioral treatments altered the penis. Sexual experience increased PWs when experience was represented by cohabitation and repeated tests to ejaculation. Tests to intromission had no effect on either measure. The PP number was not affected by ejaculation tests, however. Possibly, the PP numbers were maximal in intact males with adequate testosterone. Severing nerves to the penile area had no effect on the PP.

Androgens substantially affected the penis, but estrogens had only minimal influences. After six days of castration, the PP dropped to a 5% minimum and PWs fell to a 27% minimum. Testosterone returned both measures to intact levels. A 75 ug TP dosage maintained the PP, but 200 to 500 ug TP was required for the PW; T was about 70% as effective as TP. Only minimal increases over castrate PWs were achieved with E_1, E_2 or E_3; EB was more effective than the free E_2. PP numbers were little affected by the estrogens, noticeably less than the PW. At high estrogen dosages in combination with T, and intermediate PW was seen.

Other androgens brought the penis to intact condition. DHT(P) was equivalent to TP on both measures, and combinations of estrogen

or TP with DHT(P) were equivalent to the same dosage of DHT(P). The remaining androgens were less effective than DHT, requiring higher dosages to sustain intact penis structure. For PP number, the androgen effectiveness followed the decreasing order: androsterone, 3α-androstanediol, androstenedione, androstanedione, 3β-androstanediol, and finally hydroxyandrostenedione and HTP, which were totally ineffective. For PWs the order was: androsterone-diol, androstenedione, androstenediol, and androsterone. The maintenance conditions required a lesser dose to achieve the same PW values as recovery. The water soluble forms of androsterone proved less than half as effective as the oil soluble forms.

FM produced PP numbers rivaling those of testosterone. Only CYA and FL were able to influence androgen action. CYA not only reduced the PP numbers of T or DHT treated males, but also increased those of castrate males. However, CYA did not substantially affect the PW. FL was more effective than CYA; it reduced TP supported PP to numbers equivalent to an untreated castrate male. MER-25 and CI-628 were totally ineffective.

All the changes required time to develop. Almost a week was necessary to initiate a rise or a fall from the start of treatment, regardless of the rate of increase to intact or fall to castrate values. This was a time course intermediate between changes occurring in hormone blood levels and behavioral measures.

6.8 Introduction to the Hormone Summaries

The final three summaries are concerned with the sytemic blood hormone concentrations of Testosterone (T), Luteinizing Hormone (LH), and Follicle Stimulating Hormone (FSH). The data were generated by radioimmunoassay (RIA), and the concentrations were expressed in ng of hormone per ml of serum (ng/ml). The systemic blood was taken from a variety of sources, that included: decapitation, the jugular vein, tail vein, abdominal aorta, or cardiac puncture. The most common source was via decapitation. No consistent differences in the blood concentrations for any of the hormones due to the blood sources could be seen.

The model reports the hormone concentrations to give an indicator of the hormone level present in the rats when the behavior occurs and due to the variety of possible treatments, that may or may not affect the behavior. As described previously, the hormonal state strongly influences sexual behavior and penile structure. In the male, the primary hormone affecting the behavior is T. The production and secretion of T is controlled by LH and FSH, secreted by the pituitary gland. The concentrations of T feeds back, negatively, on the hypothalamus and pituitary and moderates the secretion of LH and FSH. Furthermore, in the body tissues, T can be converted directly to estradiol and DHT, and eventually to all of the minor androgens and estrogens.

The model attempted to reflect the hormone interrelationships. Although the model was designed to have the hormone subprograms influence one another, they do not do so very effectively. The very

poor data available for the crucial linkages between the subprograms prevented an effective working relationship.

The interaction of the hormone subprograms required two basic stages; the output of each hormone subprograms (e.g., FSH and LH) was a blood concentration, that had to be converted to an injection dosage to serve as an input to another hormone subprogram (e.g., T) or a behavioral or penile subprogram. The effects of the injection dosages of the three hormones were well supported.

However, data on the conversion of blood levels to an appropriate dosage were sorely lacking. Dose response data were no doubt developed in various laboratories, but rarely reported. Only one study was found for the relationship of T injection to blood level (139) or LH injection to plasma LH (12), and both studies provided questionable data. No dose response was available for FSH. The only exception was an excellent development of a dose response for plasma T in response to subcutaneous T implants (see T summary). Therefore, the hormone output of the model would be best considered as only an informative systemic indicator.

A couple of issues need to be considered before beginning the summaries. First, the three hormones had circadian periodicities over a 24 hour day. Therefore, the concentration of all hormones varied with the time of day (TDN). These fluctuations, however, did not directly affect the behavior, which was maintained by a hormonal state over a period of days. All the hormonal effects were assessed, as for the behaviors, with ratios of the hormone level of a treatment group compared to a control, usually intact or castrate males. In the case of variables with no definite control, such as the circadian

patterns, the samples were averaged across the range of the variable. For example, if a study took blood samples every two hours during the day, the average of the 12 data points would serve as the control value used to calculate the ratios for each sampled hour of the day. This provided the same circadian pattern, but as ratios rather than absolute blood concentrations.

As far as the TDN variable was concerned, the model used a 12L:12D light cycle, so the dark period was from TDN of 0 to 12 and the light period was from a TDN of 12 to 24 or 0. The alternative 14L:10D cycle was converted for use in the model by proportionally stretching the dark hours and shrinking the light hours. As a point of reference, sexual testing and activity were best during a TDN of 4 to 6 hours. On the other hand, blood sampling occurred during the light period in the hormonal studies reporting a specific time.

Finally, all the reference numbers presented in the hormone summaries refer to the separate hormone bibliography following the behavior bibliography. With these conditions in mind, the discussion of the effects of treatments on the hormone plasma levels proceeds.

6.9 Testosterone

The systemic blood concentrations of testosterone (ng/ml) had negligible differences between the strains; their ranges all greatly overlapped. The total range was 0.97 to 4.75 (5.58 - single outlier) ng/ml. The average of all normal adult male studies (n = 66) was 2.79 ng/ml. The concentration of T from the testicular vein was of the order of 30 times the systemic concentration (5,30,31,55,77,107,124).

Daily Patterns

Testosterone fluctuations over the course of a day were analyzed based on a ratio of the particular hour (TDN) of sampling to the average of all samplings throughout the day. The majority of males were kept on a 12L:12D photoperiod; the remainder were on a 14L:10D cycle.

The daily T patterns were highly variable. Individual males displayed zero to three peaks (maxima) or nadirs (minima)(89). Where peaks did occur, a general agreement (within 2-3 hours.) was indicated among individual males within a particular study (73,89). However, large variations occurred between studies. For example, Sprague-Dawleys (74,89,116,141) had reported major peaks at TDN = 8, 9, 16.5, & 19 among the various studies. The daily patterns were consistently repeated on consecutive days (73).

The average for Long-Evans males (18,59,73,122) was practically the opposite of the Sprague-Dawley pattern, but similar oppositions were seen within the individual studies. Data (58,67) for other strains demonstrated the same degree of opposition. Therefore, as no clear strain patterns were evident, all were averaged together.

Although the peaks occurring during the dark phase were, on the average (r = 1.43), equivalent to those occurring during the light phase (r = 1.427), the averaged curve had its maximum at TDN = 19 in the middle of the light period with a minor peak at TDN = 8 in the dark period. The nadirs were lower during the dark phase (r = 0.50) and more numerous. The primary average nadir was at TDN = 4.5, a third of the way into the dark hours, and a minor trough occurred

around lights-on (TDN = 12). Due to the effects of averaging, the maximum ratio reached only r = 1.22, and the minimum just r = 0.78. The curve fit a sine function (wavelength = 19 hrs.) with a decreasing amplitude through the light period and into the dark (TDN = 0-5).

Males kept under constant light or constant dark exhibited trimodal peaks, that were also exhibited by some males under normal light cycles (89). However, constant light or a 23L:1D cycle significantly increased (r = 1.96) the overall T level, and constant dark or a 2L:22D cycle significantly decreased (r = 0.60) the overall level (76,89).

Seasonal Variations

Differences were observed in the levels of testosterone when summer values were compared with winter values of the same group or different group of same age males (88). A T elevation occurred during the late winter and early spring (mid-Jan. to mid-Mar.). The early year surge significantly interacted with age. Only young males displayed (85-150 days old) the seasonal surge. At later ages, it did not occur. The T surge normally occurring at 60 days of age was delayed in males born during the winter. The highest T levels were attained at 90 to 100 days of age in the winter-born males. The seasonal effect proved valuable in assessing the effects of age.

Age Effects

Analysis of T concentrations from 40 to 90 days of age uncovered two noticeably different patterns. One pattern had a sharp rise up to 60 days of age and then a fall to adult levels. The other had a slower, continual increase up to 90 days of age. Although the studies did not report the time of year of blood sampling, the two patterns closely fitted those described by Mock et al. (88) as the summer, 60-day peak and the winter peak at 90-100 days of age. The model reflected those seasonal differences. The studies showing each pattern were grouped and their data averaged.

The "summer" averages reached a peak at 60 days of age (35,49,50, 51,52,77,81,88,92,122); both the rise from 40 days and the fall from 60 days to adult (90 days) closely fitted straight lines. The "winter" averages rose gradually to adult values, also, in a linear fashion (75,88,106,111,123).

The T concentration remained relatively constant from 90 to 290 days of age (7,49,75,82,88,122,123), with the exception of the early spring surge, when age and season fortuitously coincided. At later ages, T gradually decreased to a minimal level ($r = 0.36$) by 14 to 15 months of age (7,18,54,82,88). No data were available beyond 548 days (18 mos.) of age.

Behavioral Effects

Testing for sexual behavior induced a rise in the plasma levels of testosterone. With a receptive female, T started to rise with the

introduction of the stimulus female at an average rate of 0.036 ng/min. (69,72,108). The T rise reached a maximum, approximately twice the basal level, at 30 minutes or more into the test. When testing began after the male was left alone in the arena for 5 hours, the T level was already at the maximum for normal testing. However, with exposure to a receptive female, an added rise occurred to the same degree as described for males tested directly (69). The same rise occurred when the receptive female was present in the arena but the male was not allowed physical contact; however, T started to decrease earlier, at 30 minutes of testing (108).

The T rise varied based on the nature of the sexual stimulus object and the males' sexual experience. No differences between sexually naive and experienced males was evident (71,72) for T resting levels prior to testing. Following testing, naive T levels were lower than those for experienced males (naive/exp. $r = 0.71$) for all sexual objects (71,72).

Other sexual objects produced differing effects on T. T response was compared with that for receptive females at least 20 minutes after completion of a sex test. For experienced males, the effect on T induced by a sexual object followed the descending order: nonreceptive female, no contact female (separated from male by screens), female odor alone, and a male stimulus (71,72). The male stimulus was totally ineffective. The timing of the T rise to alternate sexual objects was not clear. The nonreceptive female did not alter the T from resting level up to the first PEI (71), but the T was elevated at 20 minutes posttest (72) for the nonreceptive female, near to the receptive female level. For sexually inexperienced males,

none of these stimulus objects elevated T (72). The initial rise in naive males either did not occur or T dropped back to normal levels by at least 20 minutes after testing.

Other behavioral treatments produced effects on T. Shock produced a 60% decrease in systemic T (10,47) up to 4 hours afterward. Shock or handling at an early age produced no effect on T when sampled later in life (49). The remaining behavioral variable, raising condition, had reported, contradictory results (33,56,107) and no effect was assumed.

Castration

Following castration, plasma testosterone decreased rapidly. The exponential decrease attained minimal levels (cast./intact r = 0.011 to 0.152) between 4 minutes and more than 24 hours (2,22, 50,51,52,68,116). The variability in the reported data made the establishment of a rate of decrease difficult. The better data (22,68,116), giving early measurements and short sampling intervals, indicated a rate of $e^{-3.0 \cdot CASTH(hrs.)}$ as a compromise. The equation provided a minimal T level within two hours.

Cryptorchidectomy produced only minor T decreases compared with castration. The minimal crypt/intact ratios ranged from 0.53 to 0.95 with an average of r = 0.79 (2,50,51,52,82).

Testosterone

Only one study (139), unfortunately, provided systemic T concentrations for T injections of castrate males. Plasma T at 20 hours after the seventh daily injection approximated intact levels at a 50 ug/100 g BW (125 ug/rat) dosage. T 9 to 10 times intacts was reported with 100 ug/100 g BW (250 ug) or more. When the same dosages were injected into intact males a rise was indicated at the 50 ug/100 g BW (150 ug) dosage and a five fold increase at 100 ug/100 g BW (300 ug). As these rapid T changes with increased dosage were decidedly nonlinear and the data limited (n = 5 males/group), the relationship must be considered unreliable.

Data were available on both castrate and intact males given silastic implants. The plasma T of castrated adults remained relatively constant over 36 days with 5 to 15 mm implants (123). Intact T concentrations were attained with the 60 mm T implant (23,90,96,122,123), and the rise from 2 to 60 mm was linear. Differences due to age were not clearly established (122) after 50 days of age. The rate of increase was approximately 0.045 ng/ml for each 1 mm of T implant.

Implants given intact males displayed the same rate of T increase as the castrates (8). However, the T levels were reportedly depressed at dosages of 20 mm or less (implant surface area was 10 times the length), and substantial increase was reported at 400 mm as compared with the next lower dose of 40 mm. The plasma T due to the TC (cyprionate) form was equivalent to the free T (8). With TP implants, the rate of increase due to dosage was doubled. With TP, the plasma T was depressed below the intact with 10 mm or less.

Estrogen

Estradiol effectively reduced the plasma T to at least castrate levels when injected into intact males. With multiple days of injection (7 days), EB produced minimal and usually undetectable, levels of T with more than 1.0 ug (21,137). Free E_2 required at least 10 ug to accomplish the same T depression (32).

The course of the T depression following injection of intact males was also observed. EB at 50 ug or more produced the maximum T depression by 24 hours after either a single (136) or multiple (days) of injection (21,134). On the other hand, E_2 produced maximal depression in the range of 3 hours postinjection, and T returned to intact levels by 24 hours after injection of 100 to 500 ug E_2 (21).

A comparison of the model exponents for dosage indicated a dose of EB was ten-fold more effective than the same dose of E_2. Similarly, E_2 lasted a shorter time in the systemic circulation. E_2 was ineffective by 24 hours after injection, while EB was still maximally effective at least to 24 hours.

LH and FSH

Luteinizing Hormone (LH) produced substantial increases in the level of plasma T of intact males. T rose to almost 14 times normal intact levels with 10 ug/100 g BW of LH or more. Thereafter, the level of T stayed on a plateau (91,92,93,100,101). The initial rise was exponential. No evidence was given for an age interaction (93,100,101).

The T time course following the LH injection (30 ug/100 g BW) had a definite pattern, but the two reporting studies varied some on the actual parameters. One study reported a peak at 90 minutes postinjection (92), and the other at 60 minutes (101). The peak amplitudes differed also. Following the peak, a gradual return to normal levels was indicated. The two studies were of differing strains and age, but as no effects of dosage due to strain or age were indicated, none was assumed for the time course. The two patterns were averaged, and the maximum level set by the dosage equation(s).

When EB (100 ug) was combined with LH, the plasma T was intermediate between the independent response to each hormone (91). A 1 to 3 ug LH dose was sufficient to counteract the effect of EB and returned T to intact levels. However, even with 100 ug LH, EB was capable of holding the LH induced rise to one-half its normal increase; the maximum T levels were almost three times intact levels.

Contrary to the plasma T increase to a peak at 60 to 90 minutes postinjection with LH injections of FSH (2.5-100 ug/100 g BW) produced no alteration of T (30,31,92). The lack of effect held for either multiple of single injection(s) and for young and adult males.

Human Chorionic Gonadotropin (HCG)

HCG produced substantial increases in plasma T. The T response to increasing dosage of HCG followed a logarithmic curve, at least up to 6 IU/100 g BW (47 IU/rat)(5,54). The T rise began between 0.10 and 0.75 IU and increased to approximately 7.5 times the untreated T levels with 35 IU HCG. Old male T (24-26 mos.) rose to the same

level as younger males (3-12 mos.)(54). But because the vehicle control T was significantly lower, the relative increase for old males was far larger.

After an HCG injection, plasma T rose exponentially to a maximum between 120 and 180 minutes postinjection (18,54,88,108). The falloff after reaching maximal levels was far more gradual and linear (54). The time necessary to return to normal levels was unavailable. The time course for the old males (54) was approximately the same, but the relative rise over time was exaggerated by the initial low T value. The actual patterns were about the same.

Hypophysectomy (HX)

Hypophysectomy resulted in a plasma T drop to a minimum within one day (136). The average HX/intact ratio for the 1 to 21.5 days following was r = 0.11 (6,53,55,115,136). The injection of LH (5 & 25 ug)(6,115) to HX males increased T over HX levels. FSH (20 ug) combined with 5 ug LH returned T to intact levels (115). However, FSH had no effect on HX males alone or with the high LH dose (25 ug). The 25 ug LH alone brought T to above intact level.

Several other hormones were capable of altering T levels of HX males. Prolactin (200 ug) produced only minor increases, but when it was combined with 5 ug LH, a synergistic increase to intact T levels was observed (53). Pregnenolone (2 mg), 17-Hydroxy-pregnenolone, progesterone, and 17-Hydroxyprogesterone (2 mg) failed to significantly affect the HX T levels (55).

Endocrine Glands

Adrenalectomy reduced T levels only under circumscribed conditions. A significant T decrease was reported (67) during the early hours of the light period, but not during the dark period, of the light cycle at weeks after adrenalectomy. T decreased ($r = 0.30$) between 0.5 and 2 hours immediately following adrenalectomy (116). The combination of adrenalectomy with castration caused adrenalectomy effects only within the first 24 hours. Adx + Cast produced T levels one-half those of castration alone, until after 12 hours, when no difference from castration alone could be detected (42,116).

Both thyroidectomy and pinealectomy affected the plasma T concentrations. Thyroidectomy produced a one-half decrease in T (17). Pinealectomy, on the other hand, resulted in a three fold T increase (76).

Drugs

The only data on anti-androgens or anti-estrogens was for the anti-androgen, Flutamide (FL). FL produced substantial T increases over repeated days of treatment of intact males (125). The induced T increase peaked by 5 days of treatment and decreased somewhat thereafter. However, 5-fold levels were still reported after 30 days of treatment. The maximum level was 7-fold that of the intact. As the FL effect was probably mediated via hypothalamic feedback, no effects of combinations of FL and T, TP or DHT treatments were found (68,124).

Starvation

Starvation produced an approximate one-third decrease in T level (59,60). A decrease was evident only after a full day or longer without food.

Synopsis

The systemic plasma levels of testosterone were altered by a variety of intrinsic conditions and treatments. Changes were seen due to daily patterns, seasonal changes, and behavioral treatments. The most obvious aspect of the circadian T patterns was their variability, and the resultant lack of agreement among the reporting studies, regardless of strain. The average daily pattern was damped to low amplitude changes. However, an average peak was observed in both the light and dark periods and the major nadir was during the dark. Furthermore, exposure to constant light increased T, and constant dark decreased T, overall.

A definite interaction existed between season and age. The T surge early in the year (Feb.-Mar.) occurred only in young males, males born during the late fall and winter months. Males sampled during the summer produced a significant 60 Day age peak and fell to adult levels, while the winter males had a gradual and steady rise to adult levels with their peak around 90-100 Days of age. T concentrations began to fall off by 9-10 months of age and dropped to a minimum by 14-15 months.

The introduction of the male to the sexual test arena produced a

rise in T. These effects occurred only in sexually experienced males, making these effects "anticipatory" in nature. A T elevation occurred always with an introduction of a receptive female. The elevation occurred even on top of the initially high T levels induced by prolonged exposure to the arena. Partial female stimuli (nonreceptive, no contact, or odor only) produced only partial increases in T, and no change was produced with the introduction of another male. Furthermore, shock during testing decreased T, but the condition of raising produced results too ambiguous to draw conclusions.

The majority of hormonal treatments produced changes in plasma T. Castration produced near nondetectable T levels within two hours. Cryptorchid males had lowered T, but only to a small degree. The use of T implants resulted in a linear dose response in castrates and intact males. Data were presented for T injections, but they were less than adequate and further confused by changes following injection. Implant studies established the doubled effectiveness of TP over T and the equivalence of T and TC.

Estradiol effectively reduced T to castrate levels with more than 1.0 ug EB and 10 ug E_2. Following an injection of E_2, minimal depressions were attained in the range of 3 hours following injection, and returned to intact level by 24 hours. EB had a sustained effectiveness well beyond 24 hours.

Of the nongonadal hormones, LH produced the most dramatic effects on plasma T. LH injection resulted in an almost 14 fold T increase by 60 to 90 minutes postinjection. The T level decreased thereafter. The combination of EB with LH produced intermediate results; LH prevented the EB induced decreases, or EB ameliorated the

LH rise. FSH, conversely, had no effect on the plasma T. HCG produced T increases slightly less than those of LH, with a maximum at 120 to 180 minutes postinjection.

Hypophysectomy effected a drop in plasma T to very low levels. However, the T levels tended to be slightly higher than for castration. Adrenalectomy produced a decreased T just following surgery and later during the light period, but effects due to adrenalectomy and castration were distiguishable only within the first 24 hours postcastration. Thyroidectomy decreased T somewhat, and pinealectomy increased it. Pregnenolone, progesterone, and their hydroxylated forms were ineffective. Flutamide produced a T increase in intact males over a period of days to levels rivaling those of HCG. Starvation resulted in some T depression after a day of deprivation.

6.10 Luteinizing Hormone

The concentration of Luteinizing Hormone (LH), expressed in ng/ml serum, in the systemic circulation was influenced by a variety of variables. Intrinsically, the LH concentration followed daily circadian rhythms and changes over the males' lifetime. The largest body of knowledge concerned a variety of hormonal manipulations resulting in LH blood level changes. However, initially the effects due to the intrinsic and behavioral variables were considered.

The normal, intact, untreated male LH levels were established as averages of all studies, using one data point from each study. The male strain determined the base LH level. The Holtzman strain had the lower LH concentration of 10.2 ± 3.7 ng/ml ($\bar{X} \pm SE$, $n = 10$

studies). The Wistar males were the next higher at 24.4 ± 5.7 ng/ml (n = 16). The Long-Evans and Sprague-Dawley males were equivalent at 36.2 ± 7.3 ng/ml (n = 7) and 36.3 ± 8.6 ng/ml (n = 31), respectively. The highest strain group was an assorted one; the Mixed strain LH was 50.1 ± 8.0 ng/ml (n = 12). The average of all strains was 32.5 ± 4.2 ng/ml (n = 76). A great deal of variation in the reported LH concentrations occurred within the strains. The ranges of the different strains all overlapped substantially (total range = 0.5 - 93.7 ng/ml). However, as the strain group SEs with their means did not overlap, inherent strain differences were assumed. A good deal of the variation could be accounted for by the LH-RIA assay done in different laboratories, the time of day of blood collection, and the age and condition of the male rats.

Daily Patterns

Large changes in LH through the day were consistently in evidence All the males were on a 14L:10D light/dark cycle with the lights turned on between 4 AM and 7:30 AM. The cyclic patterns during the 24 hours varied in the times the peaks and nadirs occurred. Almost all rats demonstrated one or more LH peak(s)(73,89), but they occurred at different hours. Consequently, the averages of a group of males (4-10 males) also shift among the hours from one study to the next, even within the same strain. The average of all studies utilizing a given strain established a general pattern for modelling purposes, which reduced the individual peak heights and nadir depths.

The Sprague-Dawley studies reported peaks at TDN (lights were

off for TDN = 0-10 hrs. and on for TDN = 10-24 hrs.) of about 2 (39), 5 (40), and 12 to 15 (80,116,120) hours. The strain average showed a major peak at TDN = 13 and a minor peak at TDN = 5, with the principle nadir at TDN = 21. The average curve for the Wistar studies (19,28, 86) indicated a major peak at TDN = 5.5 and a minor peak at TDN = 17.5, with a nadir at TDN = 23. The Wistar and CD (67) pattern was similar to that for the SD males. The three strains were combined for one general curve, that had a major peak at TDN = 13, a minor peak at TDN = 5, and the nadir at about TDN = 21.

The Holtzmann pattern was different. The peaks of the individual studies (58,133,143) were scattered to the later part of the light period and between TDN = 2 and 5. A very consistent nadir occurred at TDN = 9 to 10.5 in all studies. The average curve had a high peak at TDN = 4 and a nadir at about TDN = 10, at lights-on. Only a gradual increase in LH over the light period was indicated.

The SD-W pattern was approximated by a cosine function with a period of 7.5 hours for TDN = 3 to 16. The Holtzmann pattern was approximated by a sine function with periods of 15 hours (TDN = 0-8) and 9 hours (TDN = 8-12). The remainder of the patterns were approximated linearly. The peak and nadir for the Holtzmanns was substantially greater than any for the other strains, due to the averaging effect of the combined strains.

Furthermore, the cyclic changes, regardless of their nature, were eliminated when the males were castrated (80,143). This castration effect on the cycle was undoubtedly due to the higher LH output following castration.

Age

LH levels were different at earlier ages than as adults, but the differences were not consistent among the strains. The Sprague-Dawley (11,34,35,81,104) and Wistar (20,100,129) demonstrated a high variability at ages less than 55 Days. On the average, a gradual but small increase with decreasing age, at least to about 40 days of age, was present.

The remaining strains; Holtzmann (97,98,102), Long-Evans (122), and Ivanovac (51); demonstrated a large sigmoid increase from 40 Days up to the adult level (100 Days). These changes were significant.

During the adult period (90-190 Days), no consistent changes were evident (23,88,122). Mock et al. (88) males intimated a LH rise during the months of spring. Past 190 days of age, LH tended to gradually decrease (88,121). The LH concentration fell to approximately one-third the adult levels by 600 Days (almost 20 months).

Behavioral Effects

Systemic LH changed in response to sexual behavior testing and to different sexual stimulus objects. When the receptive female was placed in the test arena with the male, the male's LH concentration rose rapidly to a high point (Trt./basal level r = 2.59), and then gradually decreased over 60 minutes (69,70,72). The same response occurred in castrate males given T implants (10-25 mm T), but no change occurred in castrate males given either no T or a 5 mm T implant (70).

Furthermore, males left alone for 5 hours in the arena, prior to the female's introduction, showed the same LH release patterns as males without the prior exposure (69). However, LH had risen by the start of the test, probably due to the 10 minute adaptation period or the anticipation of the female (72).

In terms of the sexual behavior, LH had reached a maximum by the first intromission, and decreased during the ensuing behavior (71). When a nonreceptive female was substituted for the receptive female, the same LH response pattern was observed, but the increase was somewhat less (71), although not significantly.

The mating LH tended to be higher in sexually naive males than males given prior sexual experience (71,72). However, the divergence due to sexual experience did not occur when the female was nonreceptive (72). The mating LH rise also occurred when the sexual stimulus was a receptive female separated from the male by a mesh screen (no contact) or exposure to female odor only in the test arena (72), regardless of the sexual experience. When the sexual object was another male, a smaller LH increase occurred for experienced males, and no increase was seen with naive males (72).

The caging conditions after weaning had some effect on LH. The pituitary LH content (107) of cohabitant males was statistically lower than that for segregate or isolate males. A very similar LH rise occurred in the presence of a receptive female regardless of the caging condition. Furthermore, some indication had been given (126) that if males are tested during the hours of light, no LH rise occurred.

Castration and Cryptorchidism

LH rose rapidly in response to castration. A plateau was attained by 24 hours postcastration (9,117,142). When the strains; Holtzmann (2,9,46,78,142), Sprague-Dawley (3,116,118,144), Wistar (15,132), Long-Evans (117), and Mixed (1,138); were compared, no consistent differences could be seen, primarily due to the wide variation in the LH.

The LH rise following castration was biphasic. After the initial plateau (cast/intact r = 8.30) was attained by the first day postcastration, another LH rise started at approximately 7 days postcastration. The secondary rise attained a plateau by about 14 days postcastration (r = 13.8). However, the second rise was more exponential, so the approach to the plateau was more gradual than for the initial rise.

No interaction between the castration rise and age was indicated (11,50,51,57). Some of the ratios for ages of 60 Days or less tended to be higher, but the data were also more variable at these ages.

Cryptorchidism had a far lesser effect on LH. Cryptorchid males produced LH levels a little more than double the intact level (2,50, 51,102,129,140). The plateau was attained after approximately 4 days following surgery. LH rose to about the same level regardless of age, even though the intact age value differed (50,51).

Testosterone

The majority of the testosterone treatments involved injections (T and TP) for 1 to 7 days of castrate males. The LH ratios had the castration level as the control, so if effects of testosterone were evident, the LH ratio decreased from the castration high. Because no consistent differences could be seen among the strains or between the recovery and maintenance regimes, these were combined for discussion.

TP (11,24,43,44,66,85,98,105,109,128,138) depressed the LH somewhat more than the free T (119,127,128,132,139). The TP depression occurred at a lower dosage; approximately 30 ug/rat more was required to begin the T depression. The decrease in LH was exponential with a higher rate for TP than T. If the intact/cast. ratio was assumed as r = 0.120, as predicted by the castration equations (average reported value was r = 0.114 (n = 10 studies)), the TP dosage of 408 ug and the T dosage of 636 ug forced LH to intact levels.

With a subcutaneous silastic T implant, a rapid decrease in LH occurred with increasing millimeters of implant greater than the 2 mm length (23,90,96,122). Comparing the rate exponents of the implant and TP or T injection the relative doses became 18 ug TP or 27 ug T for each mm of the T implant.

A further method utilized was intravenous infusion of T (4.2 - 918 ug/day) over two to three days. The dosage required to obtain the same depression of castrate LH as injection was far lower. The dose response exponents indicated an effectiveness of infusion ten times that of injection (62).

The rapidity of the LH response to a single injection of TTP was

observed. With a single injection of 200 ug (62) or 2 mg (132) of T, the LH levels approached intact levels by 8 hours postinjection. The decrease in LH was exponential. After 24 hours, the LH was near castrate levels again.

No data were available for TP injections prior to 24 hours. However, the TP induced decrease was sustained far longer than for T. TP attained its maximum depression by 48 hours postinjection, and for doses less than 2 mg, began to return to castrate levels by 72 hours (62,66). The time course for the return to castrate levels did not appear affected by dosage, although the dosage did determine the degree of depression and the rate of return to castrate LH values after 48 hours. With 500 ug TP or less, castrate levels were attained by 72 hours (62,66). A 1.0 mg TP dose partially depressed and 2.0 mg fully depressed the LH at 72 hours (66).

When intact males were injected with T, LH was depressed. With at least 25 ug T/100 g BW (approx. 75 ug/rat/day), LH was decreased to less than one-third the intact level, often reaching nondetectable levels (29,139). The depression was accomplished within 5 hours postinjection with 2 mg T (132). However, the data were too scanty to establish any pattern of LH decrease in the intact males treated with T.

Testosterone effectively overcame the effects of castration. The injection of TP was more effective than free T, both in dosage and prolongation of effect. A single injection of T lasted less than one day, but TP remained effective for at least 2 days. Each mm length of a T implant was equivalent to approximately 27 ug of T injected per day, and infusion was ten times as effective as injection. With a sufficiently high dosage, TTP depressed LH below intact levels in

castrate males, as it depressed LH in intact males to below detectable levels.

Estrogen

Data on LH were available for estradiol, free (E_2) and benzoate (EB) forms, and estrone (E_1). Injections were given at castration or under recovery conditions. Intact males were also treated. Dose response data were available, as well as the LH time course following a single injection.

Distinct differences were seen between E_2 and EB. EB injected into castrate males on repeated days produced decreases in the castrate LH with more than 0.4 ug, regardless of the treatment regime (44,66,83,128,138). With increasing dosage, the LH decrease was exponential, dropping to intact levels (av. intact r = 0.192 (n = 5 studies)) by about 2.5 ug EB.

Although the free E_2 dose response was also exponential, a LH depression was noted only after more than 1.5 ug was injected (128). Intact levels (r = 0.30) were attained in the range of 8 to 10 ug (32,128). However, the data were too highly variable and meager to place great weight on these limits. In general, EB was far more effective than E_2 injections when given over 5 or more days. Estrone followed a dose response similar to E_2 from 0.03 to 30.0 ug/100 g BW (127), and was only slightly less effective than E_2.

When EB was given to intact males, the results were equivocal. The EB/intact ratios were found on either side of r = 1.0 across the dosages of 0.05 to 100 ug EB. No dose response pattern was observable

(21,84,91,137). The same was indicated for E_2 (132,136).

The time course of the LH decrease following a single injection of EB was similar to that for TP. LH fell to a minimum by 24 hours postinjection, and remained so to beyond 48 hours, when at least 5.0 ug EB was used. The EB castrates returned to their castrate LH levels by 72 hours (66). With very large dosages (50-100 ug EB), LH was decreased within 2 hours postinjection (132). As occurred for T, the E_2 males' LH returned to castrate level by 24 hours after injection (136). Repeated sampling over 1 to 24 hours after a 50 ug EB injection into intact males (134) showed no change from intact levels, although another study (136), with less data, reported a drop within one hour (500 ug E_2).

Substantially, EB was longer lasting and more potent with repeated injections than free E_2. Estrone was only somewhat less effective than E_2. These effects were only reliable in castrate males. In intact males, the data varied so greatly a further decrease in LH could not be assumed.

Estrogen with Testosterone

When EB was combined with TP, effects were observed at the higher dosages of both. The independent LH depressions due to EB or TP alone tended to average when combined (44). This competitive effect was observable easily at dosages greater than 0.25 ug/100 g BW (1.0 ug/rat) of EB and 15 ug/100 g BW (60 ug/rat) of TP (44,128). However, within the dosage ranges used (0.01-2.5 ug EB & 0.5-120 ug TP), the overriding effect was that of estrogen, so the ratios of

effect were closer to the EB averages than predicted by the average of the EB and TP alone ratios. A closer approximation to a pure average might have occurred if the larger, more common dosages of TP were combined with the EB dosages utilized here.

Androgens

DHT(P) was effective in depressing castrate LH to intact levels. LH began to decrease with around 10 ug DHT(P) with 5 or more days of repeated injections. The rate of LH decrease due to increasing dosage was greater for DHTP (138) than DHT (127,130). DHTP injections depressed LH to intact levels with more than 20 ug and DHT injections with more than 100 ug. The repeated days of DHTP injection pushed LH to its minimal level between 3 and 5 days of injection (138).

Several other androgens suppressed the castrate LH. 3α-androstanediol was the most effective of the remaining androgens (127, 145). Its isomer, 3β-androstanediol was only about a tenth as effective (127,145). Androstenedione followed 3α-androstanediol in degree of effectiveness. Slightly less effective was 4-androstenediol, and its alternative isomer 5-androstenediol was about a tenth as effective. DHEA and epiandrosterone were rather ineffective, and androstanedione was totally ineffective, even with 2000 ug (127). Therefore, in descending order of effectiveness in depressing the castrate LH, we had: DHTP, DHT, 3α-androstanediol, androstenedione, 4-androstanediol, 3β-androstanediol, 5-androstenediol, DHEA, epiandrosterone, and androstanedione.

Endocrine Gland Effects

Adrenalectomy did not alter LH levels in intact males (46,67, 116). Males castrated and adrenalectomized concurrently had a delayed LH rise compared with castration alone. The delay was of the order of 24 hours (116). No effect on the castrate LH was seen at later times postsurgery (44,48,116). Prolactin (150 ug) was unable to produce any change in adrenalectomized intact males (48).

Thyroidectomy produced no statistically significant changes in LH within intact males (17,40). However, several days following thyroidectomy in castrate males, LH was significantly increased (r = 1.34)(17).

Insufficient data were provided to establish a time course for the LH falloff after hypophysectomy (1) and to establish LH levels following injections of LH (12). Pinealectomy had no effect on castrate LH levels (131).

Miscellaneous Treatments

An insignificant decrease in the castrate LH was reported for injection of 2.5 mg of progesterone (16,132). A mild reduction was indicated in intact males (132). In addition, the progesterone dose did not alter any of the effects of EB (14,41,43) or TP (14,41). There was no effect of hydroxyprogesterone or pregnandione (29).

LH increased when Flutamide (25 mg) was given to intact males, but it did not reach castrate levels (125). FL did not affect the castrate LH level, showing no estrogenic or androgenic properties of FL. FL did not have a substantial effect on TP (100 ug) injected

castrates. However, another study (68) reported a significant interference of FL (6.25 mg) with the lowering of LH due to a 30 mm T implant over a period of 10 days, and a very similar interference with DHT (10 mm implant) was reported (68).

Starvation consistently reduced LH in intact males ($r = 0.71$), when starvation was extended at least 2 days (59,60,61,114). No change was induced by starvation in castrate males (60,61,113,114).

Synopsis

LH was very responsive to the intrinsic variables of age and time of day. The timing of LH peaks or nadirs during a 24 hour day were highly variable among individuals, strains, and studies. Holtzmann males, on the average, had a major peak during the middle of the dark period and a nadir around the time of lights-on. The remaining strains had peaks during the middle of the dark period and the beginning of the light period, and a nadir near the end of the light period. These cyclic changes were variations about the LH strain averages. The daily cycles disappeared in castrate males.

LH increased from 40 days of age to adult levels, except for the Sprague-Dawley and Wistar males, that had a gradual and small LH decrease to adult levels. With progression into old age, LH decreased in a gradual linear fashion.

LH rose rapidly as soon as the male was placed in the testing arena, and rose to a maximum by the first minute of the sexual behavior test. LH fell gradually during the ongoing testing. Naive males tended to produce higher LH levels than sexually experienced

males. The mating LH rise occurred even with no contact females or estrous odors alone. The rise was less when the sexual stimulus was another male. Cohabiting males had lower LH levels compared with other caging conditions.

Castration produced a biphasic increase in LH, that attained maximal levels by two weeks after castration. LH also rose after cryptorchidectomy, but not to the extent of the castrate males.

Testosterone and estrogen depressed the castrate LH to intact levels and below. TP was more effective than free T, and EB was more effective than free E_2. About 400 ug of TP and over 600 ug of T was required to reach intact level. T was effective for a little less than one day, while TP was effective over almost three days following a single injection. Testosterone was effective regardless of the delivery method - injection, implant, or infusion -, and it produced decreases in LH when given to intact males.

EB produced intact levels of LH with about 2.5 ug, and E_2 required 8 to 10 ug to attain the same effect. The duration of effect was very similar between estradiol and testosterone; E_2 lasted about the same duration as T, and EB was like that of TP. Estrone was only slightly less effective than E_2. Combination of EB and TP resulted in an averaging of their independent effects, a competitive interaction.

Among the remaining androgens, DHT(P), androstanediol and androstenedione were the more effective in depressing the castrate LH, and DHEA or epiandrosterone were the least effective, with androstanedione totally ineffective.

Adrenalectomy had little effect on LH. It only delayed the LH

rise following castration. Thyroidectomy produced LH increases only in castrated males, and pinealectomy was ineffective.

Data on several other hormonal treatments were available. Progesterone and pregnandione had no significant effect on castrated or intact males. Flutamide interfered with the operation of the pituitary-gonadal feedback. Finally, starvation depressed LH in intact males, but was ineffective in altering castrate levels.

6.11 Follicle Stimulating Hormone

The systemic blood concentration of Follicle Stimulating Hormone (FSH) was expressed in ng/ml of plasma. The average FSH concentrations for normal intact males presented no substantial differences among strains. The variation about the individual averages for each strain all overlapped, requiring the pooling of all strains. The overall FSH average was 402 $\pm$ 23 ng/ml ($\bar{X} \pm$ SE, n = 54 studies). Long-Evans and Sprague-Dawley males tended to be the lowest, and Holtzmann males tended to be the highest. These normal levels varied based on the time of blood sampling for RIA and the males' age.

Daily Cycles

Cyclic changes were evident over the 24 hour day, but the cycles varied among strains. Differences were observed between Holtzmann, Sprague-Dawley, and Wistar males. The variation among studies was high; some reported no pattern, some one peak, and others two peaks. All studies utilized a 14L:10D photoperiod.

Holtzmann males demonstrated FSH peaks consistently at TDN = 6 to 8, during the dark period, and nadirs around the time of light-off (TDN = 20-2 hrs.)(58,64,133,143). The average curve had a peak (r = 1.25) at TDN = 8 and nadirs at TDN = 22 (r = 0.875) and 2 (r = 0.92).

The FSH peaks and nadirs for Sprague-Dawleys were similar to the Holtzmann but less consistent. Two studies registered no significant pattern (40,116). The two remaining studies (67,120) had peaks in the dark period, but not at the same hours, and nadirs at both lights-on (TDN= 10) and near lights-off (TDN = 1). The average curve had a gradually developing peak at approximately TDN = 15.5 hrs. (r = 0.92), near the middle of the light period.

Wistar males (19,86) had reported peaks between TDN = 17 and 19.5, midway into the light period, and nadirs on either side of lights-off. The average peak was subtantial (r = 1.41), but no consistent nadir was evident.

As individual males had single, double, or triple peaks over the 24 hours that varied in both time of occurrence and amplitude, a random averaging of different groups of males might have produced similar differences in the average patterns, that would not be dependent on strain. This would be a reasonable basis for assuming an equivalence between the Holtzmann and Sprague-Dawley males. However, the Wistars were so divergent, with the major peak in the light period not found for the others, that they should be considered different.

Age

Differences among the strain averages were also seen for the effects of age on FSH. All strains produced a pattern of decreasing FSH from 35 days of age to an adult level, attained by 60 to 70 days of age. The major difference among strains was the initial (35 Days) FSH level and the resultant rate of decrease to adult level.

The maximal values at A = 35 provided a comparison of strains The highest maximal young/adult ratio occurred for the Wistar males (r = 3.64)(20,94,100,121,129). The Ivanovac (r = 2.10)(50,51,52), Sprague-Dawley (r = 1.90)(26,34,35,81,104), and Holtzmann (r = 1.48) (63,97,98,102) fell below the Wistars in descending order. The comparatively high response from the Wistar males was, at least in part, due to the pronounced peak seen previously during the middle of the light period; of the studies reporting the time of blood collection, all sampled in the middle or end of the light period. A gradual decrease with increasing age was indicated at least to 240 days of age (26).

Behavioral Treatments

The behavioral treatments produced no significant changes in FSH, totally unlike the increases in the LH. No FSH changes were observed over 120 minutes of sexual testing (4,69,72,126). The same held for males alone in an arena for 5 hours (4,69).

Castration & Cryptorchidism

Castration produced large increases in the systemic FSH. The increase was two stage, as occurred with LH. FSH rose rapidly immediately following castration (116) and leveled at a four fold concentration by 6 days postcastration. This plateau was sustained until an average of 28 days postcastration (range was 10-42 days postcastration). The second FSH rise was more gradual than the first, and it attained a level almost seven times that of the intact male.

All strains demonstrated a similar postcastration rise, with some amplitude dissimilarities. Holtzmann (2,45,78) and Wistar (15,129,140) males had the higher cast./intact ratios, followed by the Sprague-Dawleys (3,116,144) and others (1,138). No consistent interaction was seen with age (50,51).

Cryptorchid males also demonstrated an FSH rise following the operation. The rise was linear and gradual, attaining an apparent maximum after 7 to 8 weeks (r = 2.75). The cryptorchid level was only a little more than a third of the castrate level (2,102,129, 140). An interaction between age and cryptorchidism was not established (50,51).

Testosterone

The changes in FSH due to testosterone were established through averages of TTP/cast. ratios, where the controls were castrate males. Testosterone treatments were segregated by delivery method (injection, implant, or infusion), treatment regime (maintenance or recovery),

testosterone form (free T or TP), and comparisons of dosage or time course following an injection. No data were available for testosterone treatment of intact males.

The maintenance dosage data were the most prevalent. TP in multiple injections (44,98,128,138) produced initial FSH decreases by 20 ug doses and attained an approximation of intact levels around 200 ug TP. Injections of T resulted in FSH decreases at about the same dose level as TP, initially, but the rate of decrease over increasing dosage was far slower (127,139). T attained intact levels only with dosages greater than 1000 ug.

A similar divergence in effectiveness between T and TP resulted under recovery conditions. An initial FSH decrease was seen only after 120 ug of T or TP, noticeably more than for the maintenance condition. In addition, the T and TP forms differed, as before, in the rate of decrease over increasing dosage. TP doses of over 1100 ug were extrapolated to produce intact FSH levels (98,128). T dosages in the range of 6000 ug were expected to attain intact FSH concentrations (128,130). With TP, some increased effect was indicated with repeated injections over extended periods (> 7 days)(128).

The greater effectiveness of TP could be explained by its greater longevity in the circulation. A single injection of TP produced an FSH depression that was maximal by 48 hours postinjection (66). When the single TP dose was greater than 1.0 mg, the depression was extended to at least 72 hours (43,66). Lower dosages returned to castrate levels by 72 hours (66). The actual degree of depression was dose dependent. T tended to return to castrate levels after 24 hours postinjection (29,62,145), although at dosages greater

than 1.0 mg, an immediate return was questionable.

The data on alternate delivery systems were scant. A silastic implant containing T produced no change in castrate FSH with a dosage of 4 mm or less (96), and dosages of 40 mm or more depressed FSH to intact levels (90). These data were inadequate for a dose response curve.

Infusion of T intravenously produced an FSH depression with between 5 and 20 ug/day (62). Intact levels were attained with around 200 ug/day. Some further depression occurred with infusion on adjacent days, and FSH returned to castrate levels by 24 hours after infusion, even with dosages up to 1000 ug (62).

In summary, TP was far more effective than T in terms of the amount required to depress castrate FSH to intact levels. TP remained in the systemic circulation more than twice as long as T. A maintenance regime produced depressions with a lesser dosage of T or TP than a recovery regime. T implants were as effective in depressing FSH as injection, and infusion was more effective than T injection for the same dosage; both returned to castrate levels by 24 hours afterward.

Estrogen

Information existed for estradiol, primarily EB, and estrone. Injections were given to both castrate and intact males. However, the data were insufficient for the establishment of differences in dosage between maintenance and recovery regimes. Maintenance was the primary delivery schedule.

In castrate males, EB effectively depressed FSH (44,83,128,138).

FSH began to drop with EB dosages between 0.025 and 0.8 ug/day with multiple days of injection; the average was 0.24 ug/day. Intact levels were attained by 4 to 50 ug EB, depending on the particular study. The response to free E_2 was similar to EB, but higher dosages of E_2 were indicated (127,128) for the same effect; EB was several times more effective. Estrone (127) was approximately one-half as effective as E_2. Under recovery conditions, the maximal depression was less than under maintenance (128).

EB and E_2 were able to depress the FSH of intact males in addition. EB depressed the intact FSH to about one-half its normal concentration with 5 to 10 ug (84,137). Again, E_2 proved less effective. More than 1.0 ug of E_2 was required to cause any depression, and the one-half level was not attained even with 100 ug (32).

The pattern of FSH depression in intact or castrate males was unavailable. No significant change from the control level was observed when blood was taken 18 or more hours after an injection. Therefore, all FSH decreases were based on the dose responses, with estradiol showing depressions of FSH to intact levels in castrate males, although to a lesser extent under recovery conditions, and to the $r = 0.50$ level in intact males. E_1 was only about half as effective as E_2.

Androgens

DHT(P) given to castrate males depressed FSH to intact levels. DHT produced intact FSH levels with dosages approaching 1000 ug (127), but DHTP produced the same depression by 80 ug (138), when both forms

were injected on multiple days (5-7 days) under a maintenance regime. However, under "recovery" (DPC=5) conditions, DHT depressions were less. Intact levels were approached but not attained with as much as 6500 ug (130). The recovery depression was initiated at approximately the same dosage (≅200 ug) as maintenance, but the rate of falloff did not produce the same degree of depression. Apparently, with a single injection (2 mg), FSH returned to control levels within 24 hours (145), and no cumulative effect over repeated days of injection was observed (138) over 10 days of treatment with DHTP (5 ug).

Other minor androgens proved less effective than DHT in castrate males (127). The depression resulting from 3α-androstanediol was only slightly less than for DHT, but that for androstenediol was about one-quarter of the androstanediol depression at 1000 ug. With dosages up to 2000 ug, androstenedione, 3β-androstanediol, 5-androstenediol, DHEA, androstanedione, and epiandrosterone were ineffective.

Hormone Combinations

The effects of testosterone and estrogen tended to average when the two were combined. At lower doses of TP (0.05-30.0 ug/100 g BW) and EB (0.0025-0.5 ug/100 g BW), the average of the independent hormone treatments fit the FSH depression in castrate males very well (44). The average held for 400 ug TP with 10 ug EB (128). The results with a single injection of 1.0 mg TP with 1 ug EB (66) in castrate males and a single injection of 1.5 mg TP with 20 ug EB (26) in intact males were less consistent.

Estradiol was combined with several other hormones (29). No substantial effects were observed with E_2 + DHT in intact males. Synergism was evident when E_2 (50 ug) was combined with hydroxyprogesterone (5 mg) or pregnandione (2.73 mg) in intact males; the treatment ratio (r = 0.68) was significantly different from the normal intact FSH.

However, in castrate males, hydroxyprogesterone and pregnandione were capable of depressing FSH, and that depression was only insignificantly increased by combination with E_2 or DHT (1.5 mg). Progesterone (2.5 mg) did not alter the response to EB (14,41) or TP (41) in intacts or castrates.

Endocrine Glands

Adrenalectomy produced a small FSH decrease (r = 0.77) between 12 and 24 hours after surgery, and thereafter, in intact males (48, 116). When castration and adrenalectomy were combined the castrate rise was inhibited; however, after 24 hours postsurgery (116), no effect of adrenalectomy could be distinguished (44,48,116).

Thyroidectomy produced a significant FSH decrease (17). However, intact males thyroidectomized at 40 days of age and sampled 6 weeks later showed no FSH changes (40). In castrate males, thyroidectomy significantly increased (r = 1.85) FSH at 15 days after thyroidectomy (17).

Pinealectomy had no effect in castrate males (131). Furthermore, insufficient data (1) were supplied to establish the FSH falloff after hypophysectomy.

Starvation

The removal of food from intact males resulted in a gradually decreasing FSH concentration (59,60,61,114). The FSH decrease attained a minimum by 3 days (r = 0.69) of starvation. However, in castrate males, starvation tended to increase the castration levels (r = 1.30)(60,61,113,114).

Synopsis

The patterns of change in FSH blood concentrations closely followed those of LH with only a few exceptions. Substantial differences among strains were not evident for FSH, which were evident for LH. FSH showed changes throughout the day. Holtzmann and Sprague-Dawley males had peaks during the dark hours and a nadir around the time of lights-off. Wistar males diverged noticeably due to a mid-light period peak and a nadir around lights-off.

FSH was maximal around 35 days of age and fell gradually to adult levels. Thereafter, a gradual decrease was indicated into old age. Unlike the LH rise with exposure to a sexually receptive female in the test arena, FSH was not altered in response to any behavioral treatments.

Both FSH and LH demonstrated the two stage rise following castration. The subdued cryptorchid rise was also present. Testosterone and estrogen depressed FSH in both castrate and intact males. The longer lasting forms (TP and EB) required a lesser dosage to produce the same effects as the free T or E_2 with multiple days of injection.

The infusion method was more effective than injection. E_1 was less effective than E_2 in stimulating FSH decreases. Both testosterone and estrogen depressed FSH to intact levels in castrates with sufficient dosages, and estrogen produced depressions to half levels in intact males. Recovery conditions tended to retard the effectiveness of these steroids compared with the maintenance regime.

DHT(P) was the most effective in reducing castrate FSH compared with androgens other than testosterone. DHTP proved more effective than DHT, and again recovery retarded the effectiveness of either. The effect of 3α-androstanediol was slightly less than DHT, and androstenediol was even less so. The remaining androgens were ineffective.

The combined effects of TP and EB averaged. A synergistic effect was observed in intact males for E_2 with hydroxyprogesterone or pregnandione. Hydroxyprogesterone and pregnandione had their own independent decreasing effects in castrate males. Progesterone appeared ineffective in combination with gonadal steroids.

Adrenalectomy produced a small decrease in FSH in intact males, and only inhibited the postcastration rise. Thyroidectomy effected an FSH decrease in adult intact males, but produced an added rise in castrate males. Pinealectomy was ineffective. Starvation managed a one-third decrease of FSH in intact males and a small rise in castrates, a change similar to thyroidectomy.

Chapter 7

Theoretical Considerations

7.1 Introduction

The model of male sexual behavior described herein addressed the relationships of the intrinsic, environmental, sensory, and hormonal variables to the resultant male sexual behavior, defined by the eight behavioral measures (IL,IF,EL,PEI,EF,PE,PI,PM). The penile and hormonal measures served only a secondary role. When taken as a whole or subdivided into variable classes, these relationships shed some light on the interrelation of the behavioral measures, as well as on the current behavioral theories and the models derived from them.

If the current theoretical mechanisms adequately explained the behavior, they would be influenced, with a good deal of consistency, by the classes of variables affecting the behavior. Furthermore, these influences might be organized into model components, added to future models, that would more fully demonstrate male sexual behavior. Any redundancy among the measures reflecting the behavioral mechanisms would appear as strong correlations between the measures across a wide range of variables. The relationships between the behavioral measures provided information about the sufficiency of the theoretical mechanisms and about the potential of viewing male behavior as a single integrated composite.

7.2 Theoretical and Modelling Implications

One of the best and more current discussions of the state of the theoretic developed for male rat sexual behavior was provided by Sachs and Barfield (172). Most of the theoretical mechanisms described were utilized by recent computer models (78,197). The different mechanisms would be expected to differentially affect the behavioral measures, because several mechanisms appeared necessary to fully describe male rat behavior. The effects of the range of variables incorporated in this model should reflect the differential involvement in the behavior of the currently developed theoretical mechanisms. Knowledge of the relations of input (treatment) variables to the mechanisms would then further the development of model components dealing with intrinsic, sensory, penile, and hormonal factors influencing the mechanisms directly controlling tne behavior.

All the effects evident in this descriptive model would need to be represented in any future complete model of male behavior. The explanatory mechanisms or internal components of later models should produce results consistent with this empirical model.

Several conceptual mechanisms underlying male sexual behavior were described by Sachs and Barfield (172). The mechanisms could be paraphrased as follows:

A. An "arousal" mechanism
   It postulates an increase in a CNS activity bringing the male to approach the female and initiate or reinitiate mounting and intromission.
B. An intromission threshold
   It is a level of excitation that is sufficient for

intromission (I) behavior to occur.

C. Mechanisms controlling copulation - the control of the time repeated Is leading to an ejaculation (E).

1. The Quantal Hypothesis

The immediate, stepped excitatory increments resulting from each intromission that triggers an E when sufficient excitation (the E theshold) is attained.

2. The Nonquantal Hypothesis

It is a refinement of the quantal hypothesis to account for the enforced interval effect. It assumes an additive excitation with each intromission, but the individual excitation increments develop with time following each I, up to a maximum that dissipates over time if the next I is delayed.

3. The Temporal Hypothesis

The controlling element is the time following the first I. The threshold for E in an internally set duration, with the repeated Is sustaining the excitation level established with the first I.

4. An E gating system

This allows the release of the ejaculation behavior upon the receipt of appropriate signal(s).

D. An active postejaculatory inhibitory mechanism

The mechanism prevents the initiation of further sexual behavior for a period following each E. The inhibition after a given interval (absolute refractory phase) begins to weaken and interact with the arousal mechanism, allowing a gradual return (relative refactory phase) to the start of the next ejaculatory series.

E. A Satiety mechanism

It is an inhibitory mechanism that builds in strength gradually, lengthening consecutive ELs and PEIs and culminating in the cessation of sexual behavior. (Sexual satiety was often referred to as sexual exhaustion.)

These mechanisms should differentially affect the behavioral measures. The arousal mechanism would be expected to primarily affect the ML, IL and PEI, that measure the latencies to the reinitiation of sexual behavior. The ML would probably be the better measure of "pure" arousal, i.e., the inclination to approach and mount the female. However, the ML suffered from the lack of a sufficient data base, that was the primary reason for not including it in the empirical model.

The ML could serve a useful purpose, but not as an isolated measure. A ML/IL ratio would help decipher changes in the relationship of the underlying arousal mechanism to the ability to attain intromission. A wide discrepancy between the ML and IL, a low ratio, would indicate no change in arousal but some interference with intromission (penile stimulation), as occurred with the PNX. Higher ratios would show good correspondence between the two, signifying both were affected similarly and penile input was not the important factor. Under the latter condition, longer than "normal" ILs or MLs would demonstrate some reduction in arousal.

Because of the lack of ML data, the IL had to serve as the indicator of arousal mechanism changes, when not confounded by manipulations of penile sensation. The PEI also had an initiation component, the relative refactory phase, that comprised the last third of the PEI. As the PEI terminated at the first intromission, it also suffered from the confounding of arousal and penile input.

The copulatory mechanism(s), those controlling the intromission sequence to ejaculation, might or might not be a single independent system; however, the EL and IF would be the affected measures. The

copulatory mechanism(s) would probably interact with spacing mechanisms or inhibitory mechanisms, that extend copulation and eventually eliminate it. Copulation was totally inhibited during the PEI and a satiety mechanism elongated copulation with increasing ejaculatory series to the point of behavioral termination.

Most of the mechanisms were represented in computer models as internal components. Freeman and McFarland (78) included components for the arousal mechanism, I and E thresholds, E gating, and quantal elements. Toates and O'Rourke (197) incorporated the arousal component, I and E thresholds, PEI inhibition, and satiety effects. These models provided behavioral outputs very near those of normal untreated males.

However, neither the degree or nature of the interactions among the theoretical mechanisms was clearly established. The explanation of some behavioral observations has, so far, remained elusive. The observations included the fewer Is to E (lower IF) in the second series compared with the first, the same for the lower EL_2, the differential lengthening of the absolute and relative refractory phases of the PEI with increasing series, the dissociation of the IF from the inter-intromission interval, and the inverse relation of the IF and the intromission duration in response to enforced ICIs.

Furthermore, the effects of the variety of impinging stimulus and hormonal states on these mechanisms was not established. Were some mechanisms affected and others not by the stimulus and hormone variables, or were they differentially changed? A discussion of the effects on the measures of behavior, reflecting the operation of the theoretical mechanisms, was aided by clumping variables and their

effects into potential model components.

The effects of the variables present in the model suggested three major new components. A sensory integrator would decide the weighting of incoming sensory stimuli for sexual behavior, hopefully giving qualitative and quantitative information for the operation of the behavioral mechanisms. Although the penis provided sensory information, the information would be treated by a separate component, primarily because the penis was influenced by a variety of androgens and no direct evidence was available for hormones affecting the functions of a sensory integrator directly. The third and final component was for hormone effects, a component difficult to define. Hormonal effects might not independently affect the behavioral mechanisms, but might serve as state functions within the behavioral and penile components.

A comparison of the effects of the modelled input variables upon the behavioral measures demonstrated differential influences. Not all nor the same behavioral measures were affected by different treatment variables. The differential effect supported the establishment of the three hypothetical components. Furthermore, the results indicated which mechanisms would be affected by what variables or components. The connections of the postulated components to the behavioral mechanisms will be considered in turn, based on the effects of the relevant variables upon the behavioral measures. For greater detail concerning the individual effects of the variables, reference to the sections on each behavioral and penile measure and the listing for the direction of effects for each variable and measure in Appendix C is suggested.

Sensory Integrator

The first hypothetical component, the sensory integrator, organizes and condenses all incoming stimuli to an appropriate value or values to be utilized by components controlling the behavior. The integrator deals with the five senses, and operates independently from penile sensation. The exact, intimate workings of the sensory integrator remain unclear, as the experimental support of the "workings" is insufficient. However, a few glimmerings are available. Experimentally, the sensory data results from two different types of manipulation, removal of the sensory organ and alteration of the stimuli available to the male.

The removal of a sensory organ produced some change in all the behavioral measures. The effects of the different sensory oblations are detailed in Table 7.1 in terms of their experimental/control-sham group ratios for each measure during the first series.

The behavioral measure most affected was the IL, as the high E/C ratios showed. The EL was a close second. The IF and PEI were hardly influenced by the treatments. Decreases in the EF and PE were also evident. Specifically, olfactory bulbectomy (OBX) occasioned more change than blinding or sectioning the fifth nerve. Deafness was not tested directly, although it has been inadvertently induced by some surgical procedures. Furthermore, Beach (14) reported the removal of more than one sense organ eliminated all sexual behavior. The effects on the IL were exaggerated in inexperienced males (OBX r = 3.41 & Blind r = 6.00).

The oblation results reflected upon the mechanisms controlling

Table 7.1

The E/C Ratios* For Sensory Oblations of Sexually Experienced Males.

Oblations	IL	IF	EL	PEI	EF	PE	PI	PM
OBX*	1.76	0.86	3.60	1.25	0.62	0.57	0.77	0.77
Blind	1.00	1.00	1.86	0.86	0.88	0.42	0.62	0.62
5^{th} NX	4.76	1.00	-	-	-	0.50	0.83	1.00

* Any of the Experimental/Control group (E/C) ratios above 0.85 and below 1.20 were assumed to show no effect, as the usual range for statistically significant ratios was outside these values for most studies. Only when several studies were averaged, like for the OBX, did ratios within that range demonstrate significance.

copulation and arousal. The copulatory mechanism(s), represented by the EL and IF, was altered; the efficiency of the temporal element was retarded. The effect on the arousal mechanism was not as clear. The PEI was not strongly affected, although the IL was. A definite lengthening of both would have been more conclusive.

The ML rather than the IL would have been the better measure of arousal. Perhaps the ML would have remained unchanged like the PEI, demonstrating no arousal effect. However, the ML data (85,168,185) were too poor to draw conclusions, and no reliable intra-study comparison of the ML and IL was available. A decrease in the effects on the IL with sexual experience suggested the inclusion of a learning element in the sensory integrator.

The satiety mechanism was probably stimulated by sensory oblation. Reduction of sensory input tended to decrease the EF and definitely decreased the PE and PI. Whether the satiety and copulatory mechanisms interact was open to question, but the reduction in sexual activity was evident; the males stopped earlier and fewer responded.

No evidence for a hormonal influence on the sensory integrator existed, due to a paucity of experimental effort. Larsson (137) indicated that neither high levels of TP nor LH with FSH produced any further behavioral change in the OBX males. However, Larsson was the only experimenter to use a combined treatment and report it. In addition, no strong theoretical reasons could be found for assuming hormones had a direct effect on sensory integration.

When the sensory organs were left intact, the quality of the stimuli presented to the male in a sexual test arena influenced the

measures of behavior. The stimuli were categorized into those pertaining immediately to the female and those to the general environment.

The female stimuli included the degree of sexual receptivity displayed, the activity of the female, and the substitution of other sexual objects as the focus for copulation. A fully receptive, estrus female was required for the display of normal levels of male sexual behavior. Few males would attain intromission with active nonreceptive females, but they did mount regularly. However, the reduction in female stimuli were confounded with changes in the female's behavior - nonreceptive females would often repulse the male. Similar low levels of behavior occurred when other males, guinea pigs, or an immobilized receptive female were presented as sexual objects. VAGX (receptive female with a closed vaginal opening) females produced a reduction in the IF and the EL in the reduced number of males responding. The ML, IL, and PEI were unaffected. The interference with vaginal intromission apparently influenced the copulatory mechanism only, or the experimental VAGX selected for those males performing more rapidly and with fewer Is. Substitution of a new stimulus female at sexual satiety reinitiated copulation, but did not substantially alter the behavioral measures relative to the last complete series. Classical conditioning paradigms using access to a receptive female as the unconditioned stimulus showed no consistent patterns among the measures. The best assessment was that stimuli other than those from a normal receptive female reduced the efficiency of copulation.

The blood hormonal changes due to exposure to various sexual

objects were more sensitive to the differing stimuli. LH and testosterone levels increased during sexual testing with various sexual objects. The height of the LH surge at the start of testing discriminated among the stimuli. Obviously, the receptive female produced the highest LH peak, but the nonreceptive female also produced a high peak. The peak was lower for a receptive female physically separated from the male (no-contact) and for the presence of estrus female odor alone. A male stimulus or handling had even lower levels. The LH peak changes indicated arousal changes, because the surge occurred at the very beginning of testing, before the first intromission.

Similar results were obtained for testosterone. The T rises in the presence of a receptive, nonreceptive, or a no-contact female were equivalent. However, after 40 minutes, the increased T levels were not sustained with the nonreceptive and no-contact female. The presence of female odor did not induce as high a T increase and a male stimulus was even less effective.

Therefore, some discrimination of the stimulus content occurred, which then stimulated a relative LH release, inducing a later secretion of testosterone. The relative stimulus intensity of the sexual object would be: the receptive female (100%), nonreceptive female (90-100%), no-contact female (80%), female odor only (70%), and another male (45%), based on rough estimates of relative changes in LH and T. These could be the values passed to the arousal mechanism.

The environmental stimuli tested were a hodge-podge, but they indicated some sensory integrator functions. The "excitatory" stimuli, i.e. group testing, observation of a copulating pair prior

to testing, handling, and moderate electric shock, had differing effects. The most consistent was an EL decrease in all cases. The EF was increased, in most cases the IF decreased (group Ts, handling), and the PEI decreased (handling, shock). The IL was inconsistent. In addition, the group tests and handling produced effects primarily in old males; the younger males were usually unaffected.

Apparently, the copulatory mechanism(s) were stimulated to greater effectiveness by the "excitatory" stimuli, resulting in decreases in both IF and EL. Theoretically, the excitation (quantal) for each intromission was increased, the time necessary for E (temporal) was reduced, the E threshold was lowered, or a combination of the three were possibilities. The influence of the satiety mechanism was reduced, as indicated by the increased EF and PE. If the satiety mechanism operated directly or indirectly on the other behavioral mechanisms, an improvement in the IF and EL, as well as a reduction of the PEI and IL representing the arousal component would be expected; however, the measures representing the satiety and copulatory mechanisms were more strongly influenced than those for the arousal mechanism.

The excitatory changes had a learned element. Males entrained to a shock avoidance paradigm - linked to copulation with the female - showed the same changes in behavior as males given shock during testing. However, if the trained males were tested in a novel arena, the effects of the learned shock excitation disappeared. The behavioral changes were self-induced, based on an "expectation" of shock. The learning element was further supported by the reduction in the IL of naive males given repeated sexual experience. The other

measures were not altered by experience. Sexual experience seemed to affect only the arousal mechanism.

When noxious stimuli were presented, such as high painful shock levels or a loud noise during testing, the reverse of the excitatory changes were seen. The IF and EL were increased along with the IL and PEI; EF and PE decreased. High shock stimulation was intense enough to nearly eliminate intromission. Sexual arousal was depressed, and satiety stimulated; the efficiency of the copulatory mechanism(s) was reduced. The possible interaction of the satiety mechanism with the others was again indicated.

Electroconvulsive shock (ECS) had different results. ECS increased the IL and PEI and decreased the IF and EL, depressing arousal and stimulating copulatory mechanisms. The ECS, however, was not a manipulation of stimuli, but an over-stimulation of all cortical areas. The effect was not consistent with the removal of one sensory modality.

In general, the hypothetical sensory integrator would have two major elements. The effects of sense organ removal would result in quantitative decreases in the output of the component, with a total elimination of output for multiple sense loss. This decreased output would produce debilitating effects on the behavioral mechanisms; the result would be an elongated IL and EL, a retardation of the copulatory mechanism, a decreased EF and PE, accelerating satiety, and a tendency toward increased arousal (IL,PEI). The effects of impinging stimuli were more qualitative in nature. Considering both behavioral and LH and T effects, the stimuli represented by a receptive female were optimal. The lesser stimuli; non-receptive female, no-contact female, female odor, and a male, in descending order; were discriminated well

by LH and T rises, but poorly by behavioral measures. The effects of the environmental stimuli could be expressed as an inverted U-shaped function - low to moderate stimulus intensities, as the excitatory stimuli, stimulated sexual behavior, but more intense stimuli, as the noxious stimuli, retarded the behavior. In addition, the weighting of stimuli should be alterable due to repeated exposure to a stimulus; learned associations would particularly influence the arousal mechanism.

Penile Component

An independent penile component was separated from the sensory integrator for two basic reasons; the penis was very sensitive to hormonal conditions, unlike the integrator, and the sensory integrator dealt with stimuli received from the males' environment. The effects of neural output from the penis were assessed by sectioning nerves innervating the penis and by penile anesthesia. Several androgens were capable of supporting the penile structure.

Sectioning the Pudendal or Dorsal Penile nerves produced increases in the IL and EL. The IF was unaffected, and the PEI increase as questionable. The EF and PE showed large decreases.

Apparently, PNX had little or no effect on arousal, which was expected as neural feedback for the penis would occur primarily during intromission. This was supported by the basic lack of change in the PEI and ML (118,142,150,198 & Vomachka, pers. com.). The IL increase was evidently due not to the arousal stimulated approach and mounting but to the reduced ability to attain or perceive intromission.

The result of reduced input to the copulatory mechanism, the increased EL, was to extend the temporal element. As the IF was unchanged, but the time required for each I was increased, a quantal explanation was unlikely. The strong PNX reduction of the PE, but little effect on the PI, indicated the lack of penile sensory input to the CNS might prevent the attainment of the E threshold (possibly set to a higher level) or the trigger of an E gate in most males.

The satiety mechanism was strongly stimulated, as the EF fell to a minimum ratio of $r = 0.18$. As the EF was reduced five fold and the EL increased three fold, some interaction between the mechanisms controlling copulation and satiety was again indicated. However, the satiety effects did not appear to directly affect the arousal mechanism.

Penile anesthesia complemented the PNX results, but anesthesia was not a particularly good experimental treatment. Anesthesia eliminated ejaculation and most intromissions, but as with PNX, no change occurred in the ML (83).

The presence of androgen was required for maintenance of the penile papillae, that maximize stimulation of the sensory receptors on the penis. Testosterone, DHT, androstenediol, androstenedione, androstanedione, androstanediol, and the nonsteroidal androgen, FM, all influenced the papillae. TP, DHT, and FM, however, were fully effective. PNX did not influence the plasma hormone levels. When the hormonal support was removed by castration, the reduction of sensory penile information was not immediate. The papillae remained normal for about 6.5 days, and then regressed over a period of two weeks. The return to normal condition with injections of the

stronger androgens was almost three to four times slower than the castration regression. Therefore, the penile component would reflect the gradual change in output with hormonal treatments. However, the penis was not the only component affected by hormones.

Hormone Component?

The utility of an independent hormone component was questionable. Time lags, measured in days, were required for the gradual development of hormone effects. Nonhormonal behavioral and penile changes and implied influences of the controlling mechanisms developed over substantially shorter time periods. Because of the time discrepancies, hormonal effects might be treated better as state functions within each of the behavioral, sensory, or penile components. A hormonal state assumes no hormone induced change during each individual sexual test. The state would be capable of shifts only between tests.

In addition to the conceptual problem, the scattered available information needed for the model relationships was a problem. Often, the time courses for the development of hormone effects were not reported, only the test averages. Furthermore, dose responses within the submaximal dosage ranges were rarely reported. For example, the data on TP injection had very few studies (28,32,49,60,177) with multiple doses, with at least one dose less than 100 ug - the approximate minimum dosage for normal behavior maintenance. The studies did not provide the time courses for the doses for any of the frequency or latency measures. The combination of multiple lower

dosage and time course were reported (32,49,177) for the PE and PI, only.

The remaining problem was one of analysis. When a hormone was removed, the number of males responding decreased over time, so fewer and fewer males provided values for the behavioral measure averages with increasing time. These averages were compared with pretest scores for the entire group or with the averages from concurrent control groups. In neither case was any account taken for changes in the experimental male group means due to the selection for males with greater sensitivity to the hormone treatment or greater behavioral endurance. This was of particular import when the measure under consideration, e.g., the PEI or IF, demonstrated their major changes just before the cessation of behavior. Analysis procedures need not be changed, as the experimental regimens leave few options, but the reporting of the pretest scores of the males that were the last to cease responding - those that most influenced the establishment of the pattern of change over time should be included in articles.

Regardless of the difficulties, general hormonal effects could be loosely grouped into those involving CNS action and those primarily involving peripheral action. The theory that testosterone aromatized to estradiol, that acted centrally to influence behavior, and testosterone was converted to DHT and other androgens, that act peripherally to maintain penile and spinal structure or activity supporting sexual behavior, was the basis for the categorization. The generalities were consistent with the differential effects of the variety of hormones included in the model and their influence on the postulated behavioral mechanisms.

Hormone comparisons rather distinctly separated the behavioral measures believed to govern the copulatory and arousal mechanism. Changes in the IL and PEI were consistent with no change in the IF and EL; the inverse held as well. The effects on the EF, representing a satiety mechanism, were also discriminative.

Castration demonstrated the hormonal influences on the satiety mechanism. The EF and IL were the most sensitive to the lack of testicular hormone. Measure comparisons were made using a half-point value, that was the value for the variable under consideration, when the E/C ratio was half way between, in this case, the intact and long-term castrate ratios. The half-point (HP) for CAST for both EF and the IL was approximately 9 days. Nine days was also the HP for the penile papillae, suggesting that penile input restrained the satiety mechanism. The remaining behavioral measures produced much longer HPs: respectively; 44, 56, & 70 days for the PEI, EL & IF; the PE-PI HP as 14 to 15 days.

Apparently, the critical influence was the output from the penis, which decreased rapidly with time following castration. The penile sensory output reduction made the attainment of intromission more difficult, elongating the IL, and effecting a similar drop in the number of males capable of attaining I or E, thereby lowering the PE, PI and EF. Little evidence of effects on the arousal mechanism was observed, because the PEI was affected only when most males ceased copulating. The IL was too closely tied to the penile output for conclusive assumption of arousal effects, and the data for the ML were scanty and inconclusive. The EL effects were more likely linked with the declining ability to attain I than copulatory mechanism changes,

because the IF remained stable up to the cessation of behavior.

Androgens other than testosterone acted primarily at peripheral sites. DHT, androstenediol, androstenedione, and FM caused increases in the IL and PEI, but did not affect the IF or EL. These androgens had demonstrated effects on the penis, and DHT had a definite maintenance effect on the spinal reflexes (94). Therefore, the androgens maintained the penile output necessary for the sequencing of sexual behavior controlled by the copulatory mechanisms, at least to the point of behavioral cessation. The androgens were not capable of maintaining the activity of the arousal mechanism.

Estradiol produced effects opposite those of the androgens. Estradiol increased the IF and EL, and had little or no effect on the IL and PEI, in spite of extremely low EFs and PEs. As estradiol was believed to act centrally, and had no effect on penile tissue, penile output was drastically reduced and the copulatory mechanisms were not sustained. Estradiol did appear to maintain the arousal mechanism, that does not require penile information. An effect of estradiol on the satiety mechanism was unassumable, as the sexual behavior was severely curtailed (see EF and PE summaries). The E threshold may have been raised so high that E could not be attained, or the E gating may have been blocked. Probably, the I threshold was also raised, as well as, possible retardation of quantal and/or temporal elements may have occurred. Therefore, estradiol could adequately support the arousal, but was insufficient for nominal copulatory mechanism operation.

When the hormones could be segregated by central and peripheral operation, as with EB or DHT, distinct differences occurred among

the hypothesized mechanisms. However, when hormones had both central and peripheral activity, such as testosterone or hormone combinations like the DHT and EB combination, all clarity of effect disappeared.

With the injection of testosterone, all measures were affected. The IF was influenced the least, but all measures attained an approximate of normal intact response between 50 and 100 ug TP. The penile papillae were more sensitive to TP than the behavioral measures. However, clear differentiation among the measures was not possible.

A similarly opaque picture developed with combinations of estradiol and DHT(P). The available dosage ranges produced either approximately normal intact responses (usually 200 ug DHT) or discrepant results. The IL and IF were not affected; the PEI had a questionable increase with EB, but not the E_2 form, and EL decreased with E_2 but not with EB.

The differential effects of the hormones supported the central and peripheral distinctions; the hormones could act to influence CNS function or the sensory output from the penis. DHT and some of the minor androgens affected the peripheral structures, primarily, resulting in the maintenance of the operation of the copulatory mechanisms, but not the arousal mechanism. Estradiol, acting only centrally, maintained the arousal mechanism, but not the copulatory mechanisms. Single hormones, such as T, and hormone combinations, such as EB and DHT, that act both centrally and peripherally, resulted in no differential measure-mechanism effects.

This did not imply the mechanisms controlling behavior were located either in the CNS, penis or spinal cord, but that the

hormones maintained the activity of tissues, neural or otherwise, that support the activity of the proposed mechanisms or components. The explicit connections between the penile, sensory, hormonal, and behavioral elements influencing or controlling the ongoing sexual behavior remained to be fully established.

Synopsis

Although the current development of theoretical mechanisms for the control of male sexual behavior do not explain all aspects of sexual behavior, they are sufficient to demonstrate relatively normal behavior when modelled. On the other hand, the intrinsic, stimulus, sensory, behavioral and hormonal variables influencing sexual behavior have not been systematically merged into the current theory or models. Components, such as a sensory integrator and penile component, and hormonal elements fill that void (see figure 7.1).

Because the IF and EL reflect the operation of copulatory mechanisms, the ML-IL and PEI reflect the arousal mechanism, and the PE-PI and especially the EF reflect a satiety mechanism, the connections of the new components to behavioral mechanisms can be indicated. In the sensory integrator, the quantal elimination of sensory input by sensory organ oblations retarded the operation of copulatory mechanisms, particularly the temporal aspect, possibly retarded the arousal mechanism, and stimulated the satiety mechanism. Learning elements were required, at least, for the arousal connection, and two or more oblations zeroed the integrator, eliminating the behavior. The stimuli representative of the sexual object

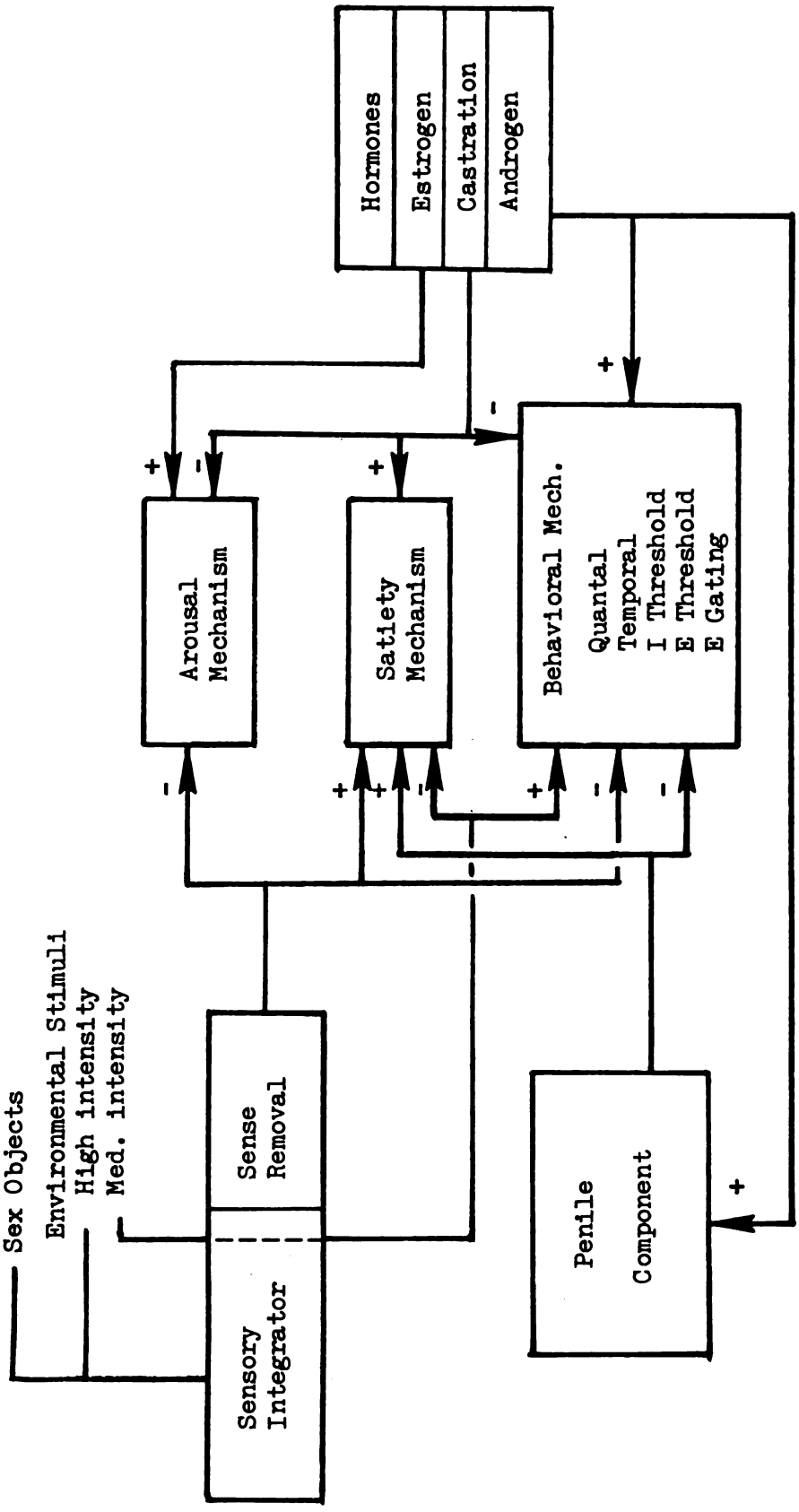

Figure 7.1 The Relationships of Hormone, Stimulus, Sensory, and Penile Components or Elements to the Arousal, Satiety, and Behavioral Mechanisms. The signs indicate the direction of change induced upon the mechanisms.

presented a gradation from a fully receptive female to another male, which influenced arousal and probably indirectly showed rapid elimination of copulation mechanism activity with stimulus divergence from the receptive female. The environmental stimuli demonstrated an inverted U-shaped relationship; moderate, excitatory stimuli stimulated the copulatory mechanisms and retarded satiety, and more intense, noxious stimuli accomplished the reverse. These stimuli had little effect on an arousal mechanism, and a definite learning element was present.

The reduction of output from the penile component, due to PNX or anesthesia, had little effect on arousal, but retarded the copulatory mechanisms, primarily the temporal element and E threshold or E gate, and strongly stimulated the satiety mechanism. Unlike the sensory integrator, the penile component required hormonal support. A gradual decrease, over days, in penile output occurred with elimination of androgen support and returned from zero levels with androgen addition. The increase with androgen supported recovery was three to four times slower than the regression decrease following castration.

Whether hormonal effects are handled by a separate component or as elements of the behavioral mechanisms, the results supported separation by central and peripheral effect. The IL and EF, representing the arousal and satiety mechanisms, and penile papillae were the most sensitive to testicular hormone elimination at castration. DHT and other minor androgens, acting primarily at peripheral sites, maintained normal operation of copulatory mechanisms but not the arousal mechanism. Estradiol, acting centrally, produced the opposite result; it maintained the arousal mechanism and not the

copulatory mechanisms. Hormones, such as T, and combinations, such as EB and DHT, with both central and peripheral activity, usually maintained normal function of all mechanisms, and at low dosages all mechanisms were affected just prior to behavioral cessation. The state of hormonal maintenance of the copulatory mechanisms would override all influences of the sensory integrator and penile components.

7.3 A Composite Male Sexual Behavior Measure ?

A composite male sexual behavior measure, that indicated an effect if any one of the separate measures demonstrated an effect, could not be clearly established. Based on the association among the male measures, the significance of each measure could be implied relative to the copulatory behavior as a whole. The relative number of effects demonstrated by each measure and the correlations between the measures also aided the search for the composite.

Several general formulations were utilized to make comparisons among the behavioral and penile measures. The first formulation was a measure by measure correlation analysis using Kendall's Coefficient of Rank Correlation (182), presented in Table 7.2. The correlated values were the maximum or minimum E/C ratio values attained in the model over specified variable ranges for each measure. The second general measure was a compilation of the reported occurrence of experimental effect and its direction (see Appendix C). To compare measures, counts of the number of times one measure showed a change and another changed in the same or opposite direction for the same

treatment variable were taken. The total number of measure to measure comparisons, i.e., with data to make comparison, were presented in Table 7.3. In Table 7.4, the number of times two measures were affected in the same and opposite directions were listed. Table 7.5 showed the ratio of the majority group, either same or opposite direction change, to the total possible comparison number (Table 7.3).

The final formulation, a sensitivity indicator (Table 7.6), utilized counts within each behavioral measure, rather than between. The number of reported effects were given as counts and expressed as a ratio to the total number of variables with data support. They were organized by variable class. The basic assumption of this compilation was simplistic - the more treatment conditions capable of inducing a measure change, regardless of its direction, the more sensitive that measure was. The relative number of effects was consistent across the different variable classes, with the one exception of the drug variables. Effects reported as statistically nonsignificant ($p>.05$) were counted as no change.

If the behavioral mechanisms were valid, a composite could be composed of one measure representing each theoretical mechanism. Either the IF or EL, the ML (or IL) or PEI, and the EF or PE would be possibles. The IF was the best candidate for elimination from contention due to the redundancy. The IF was the least responsive to all treatments - it had the lowest sensitivity ratios (Table 7.6), it did not correlate with any of the other behavioral measures (Table 7.2 - the IF was the only measure without statistically significant correlations), and it was the least consistent measure (Table 7.4 -

Table 7.2

Correlations Between the Behavioral Measures.

Measure	IL	IF	EL	PEI	EF
IF	-.06				
EL	+.56***	-.04			
PEI	+.31***	-.05	+.44***		
EF	-.52***	+.11	-.44***	-.34**	
PE	+.01	+.02	-.29***	-.09	+.29*
	IL	IF	EL	PEI	EF

* p < .05
** p < .01
*** p < .001

Table 7.3

Total Behavioral and Penile Measure Comparisons.

Measure	IL	IF	EL	PEI	EF	PEPI	PP
IF	71						
EL	67	77					
PEI	64	76	79				
EF	34	49	38	40			
PEPI	64	86	74	81	44		
PP	18	23	22	27	14	33	
PW	16	20	22	22	11	23	20
	IL	IF	EL	PEI	EF	PEPI	PP

Table 7.4

The Number of Same and Opposite Direction of Effect (Same/Opposite) for Measure to Measure Comparisons of All Variables.

Measure	IL	IF	EL	PEI	EF	PEPI	PP
IF	6/20**					X^2 Statistic	
EL	32/5***	17/18				* p<.05	
PEI	26/8***	11/17	27/11**			** p<.01	
EF	3/18***	17/9	2/22***	3/18***		*** p<.005	
PEPI	6/33***	37/6***	10/37***	8/33***	28/1***		
PP	0/7***	11/1***	2/7	1/9*	9/0***	12/1***	
PW	1/7*	9/2*	2/10*	0/9***	6/1	12/0***	9/0***
	IL	IF	EL	PEI	EF	PEPI	PP

Table 7.5

The Ratio of the Major Same or Opposite Measure Correspondence to the Total Possible Number of Comparisons.

Measure	IL	IF	EL	PEI	EF	PEPI	PP	PW
IF	.282							
EL	.478	.234						
PEI	.406	.224	.342					
EF	.526	.347	.579	.450				
PEPI	.516	.430	.500	.407	.636			
PP	.389	.478	.318	.333	.643	.364		
PW	.438	.450	.455	.409	.545	.522	.450	
Beh. AV	.442	.303	.427	.366	.508	.498		
All AV	.434	.349	.415	.367	.533	.482	.425	.467

Table 7.6

Sensitivity Indicator:
The Ratio of the Number of Significant Effects to Total Treatment Conditions.

Variable Class	Change/Total counts						
	IL	IF	EL	PEI	EF	PE	PI
Intrinsic	7/10	1/10	6/11	6/11	5/10	7/10	5/8
Beh. & Stim.	12/23	21/35	12/23	11/23	10/17	22/26	7/16
Sensory	8/10	5/11	7/8	4/7	5/7	11/13	11/14
Gonadal Horm.	6/10	7/15	9/15	11/17	6/7	23/27	22/26
Androgens	7/12	5/9	7/11	13/19	1/5	17/28	14/19
Drugs	3/12	4/16	4/14	4/16	2/3	10/24	8/19
Non-Hormonal	27/43	27/56	25/42	21/41	20/34	40/49	24/38
Hormonal	13/22	12/24	16/26	24/36	7/12	40/55	36/45
All	42/77	43/96	45/82	49/93	29/49	90/128	67/102
	Sensitivity Ratios						
Non-Hormonal	.628	.482	.595	.512	.588	.816	.605
Hormones only	.591	.500	.615	.667	.583	.727	.800
Drugs	.167	.250	.286	.250	.667	.417	.421
All (no drugs)	.615	.488	.603	.584	.587	.769	.711
All	.545	.448	.549	.527	.592	.703	.657

the IF had an equal distribution in direction of effects paired with the other measures). The poor directionality of IF effects, no doubt, caused the lack of correlation with other measures. Sachs and Barfield (172) also considered the IF highly stable.

The remaining measures, excluding the PE, showed good correlation among one another (Table 7.2), indicating a reasonable degree of unity. The propensity for their effects to be in the same direction among the IL, EL, and PEI, and the opposite direction for EF comparisons was significant in all cases (Table 7.4). Although the IL, EL, and PEI were similarly affected, little distinguished one from another. The PEI was somewhat less sensitive to change than the EL and IL, and the IL was the more labile, to minor degrees. The three were consistent across the different variable classes (Table 7.6). The correlations (Table 7.2) among the three measures were all significant, but not large enough (better than $\pm$ 0.80) to assume redundancy and eliminate any one from contention. Similarly, the EF correlated with the three latency measures to about the same degree, but inversely. The EF could not be reasonably eliminated either.

Unexpectedly, the PE, representing all the responding male ratios because of its greater lability, proved the most responsive measure of all behavioral measures. It was the most likely to change in response to experimental treatments, which was demonstrated by its higher sensitivity ratios (Table 7.6). The PE had significant directional pairings with all other measures (Table 7.4), but when the magnitudes of effect were correlated, the PE correlated poorly with all measures (Table 7.2), indicating substantial independence. The PE was more sensitive than the EF, but as the correlation was

poor, the PE evidently did not reflect the same mechanism(s) of action; the PE might have represented satiety effects, in part, but certainly not in total. The PE seemed more an indication of behavioral degeneration as a whole rather than inhibition or stimulation of particular behavior control mechanisms. The general degeneration was most noticeable under conditions that halted copulation by the first ejaculation - where satiety effects could not be observed, as when penile neural output was eliminated.

The degrees of redundancy were based on the correspondence (Table 7.4) of the parallel direction of effects or their opposition in two measured comparisons. The EF and the PE or PI were the most alike, demonstrated by the correspondence ratio of 0.636 (Table 7.5). In addition, the EF followed by the PE-PI showed the higher correspondences with all the other measures, as indicated by the average correspondence ratios of 0.508 and 0.498, respectively. This gave a further indication of an involvement of satiety with all the other behavioral mechanisms. As expected, the imperturbable IF had the least correspondence with the other behavioral measures.

In the beginning, the elimination of one or more behavioral measure(s) was anticipated. However, the level of correspondence was not sufficiently high to warrant the elimination of any one measure from a composite male measure. Even when the parallel lack of effect (no change in two measures) correspondence was added to the directional correspondence, the average correspondence ratio for the EF and PE-PI were 0.662 and 0.652, respectively; not a substantial improvement.

Therefore, the only measure that might be discounted in the activity of a composite sexual behavior measure was the IF. The lack

of change to a variety of treatments helped little in the elucidation of underlying operations. The fact of the IF stability was, however, noteworthy.

As the correlations between measures were too similar to distinguish their relative importance and a reliable mathematical composite would require clear definition of relationships, only the very general relationship could be put forward. The general form of a composite would probably follow:

$$\frac{(IL)(EL)(PEI)}{EF} + (PE\text{-}PI\text{-}PM)$$

The latency measures were interrelated by the correlations, and the inverse correlation with the EF was also indicated. No indication of differential relations was found among the different variable classes. The weighting of the four factors would require further study. The PE and its cognates were related differently to the other measures because the correlated effect was poor, and its reflection of a more general behavioral effect was indicated. Furthermore, the PE's demonstrated sensitivity would require a heavy weighting. Although the given results did not conclusively define a male sexual behavior composite, the demonstrated interrelation of the behavioral measures indicated that a composite male measure could be developed.

APPENDICES

APPENDIX A

APPENDIX A

The Input Variables

The input variables have been categorized into eight divisions, established by variable type and program organization. The intrinsic variables refer to the variables determining the normal intact male rat. The test variable category defines the test situation. The experimental variables deal with a variety of manipulations of the males' behavior, sexual object and environmental stimuli. The next division is the sensory variables. The remaining divisions deal with various hormonal manipulations, including a division for the major gonadal hormones (castration, testosterone, and estrogens), the minor androgens, nongonadal hormone treatments (primarily pituitary hormones and endocrine gland removals), and the grouping of anti-androgen, anti-estrogen, and aromatase inhibitor drugs with an additional few miscellaneous variables. Each division includes both real continuous variables and integer controller variables; fixed point designations should be assumed unless integer values are a stated requirement.

I. Input Variable Descriptions

A. Intrinsic Variables

ST - The male rat strain (integer): 1= Göteborg (G), 2= Long-Evans (LE), 3= Sprague-Dawley (SD), 5= Mixed strains (M), 6= Holtzman (H), 7= Israeli

SR - The number of the ejaculatory series (not a designated variable).

NSR - The maximum number of calculated ejaculatory series (preset at 5.0).

A - The age (days) of the males from birth (200 days is preset).

YMON - The month of the year of testing. The months are designated from 0.0 to 12.0, referring to the beginning of January to the end of December (1 day ≅ 0.033).

B. Test Condition Variables

TNO - The number of the test in a series of repeated tests.

TDN - The hour of the start of the sexual test during a 24 hour day. A light cycle of 12L:12D is assumed (the dark period is 0.0 to 12.0 hours and the light period is 12.0 to 24.0 (0.0) hours.).

LTPER - The alternative light cycles ranging from constant dark (0.0) to constant light (24.0) (preset at 12.0(12L:12D)).

TBT - The number of days separating repeated tests.

TMIN - The test length in minutes measured from the introduction of the female to her removal. (Sexual satiety is assumed greater than 120 minutes.)

COPMIN - An exact time during the test: the number of minutes into the test from the introduction of the female to the test arena (cannot be longer than TMIN).

SEXEXT - The number of tests of sexual behavior given previous to the current experimental test. The sexual experience includes naive males (0.0 tests) to experienced males (4.0 or more tests).

NRACOND- The condition of caging during early development, usually from weaning to 90-100 days of age. The integer values include: 1 = isolation - housed alone
2 = cohabitation - with both males and females
3 = segregation - with a group of males

TDRAIS - The age in days at the initiation of the NRACOND caging condition. Weaning provides a convenient marker at approximately 30 days of age. However, the treatment can begin as early as 2 days of age.

C. Experimental Manipulation Variables

SCREEN - The controller of a special caging condition where the male or female rat(s) are separated from the experimental male by a double wire mesh screen, that prevents physical contact. This is an alteration of the NRACOND conditions. Any integer greater than 0 activates it.

EICI - The length (min.) of the enforced interval between intromissions.

NEICI - The controller for the type of experimental use of the EICI. The female (0 or 1) or the male (5) can be removed from the arena. The EICI can be instituted after each intromission (10) in a series or only after a single designated intromission during each series (1 or 5) or after all Is out to and including satiety (50).

NPI - The number of intromissions before any manipulation is made (used in conjunction with NEICI = 1 or 5).

EPEI - The length (min.) of the enforced interval initiated following ejaculation. The male is denied access to the female for the designated period.

NFRESH - The controller for a change of the stimulus female. The replacement female could have no immediate prior copulatory experience (Fresh) or have had experience (Used) with another male. The female may be changed at each ejaculation (1), at satiety (10), at satiety but handled at each ejaculation (20), or at both each E and satiety (25).

ISHOCK - The integer controller for stimulation by electrical shock. The shock was applied to the flank, tail, or back by an attached wire or through the feet via an electric grid floor. The intensity and duration of the shock varied, usually shock was set at just below the squeal level for each rat (10). Otherwise, the shock was set at a significantly higher level (5).

ISS - The integer controller for the intensity of the delivered shock. The intensity is altered by adjustment of the number of shocks (20 = 10-20 shocks/min.) or the duration of shock (1 = 5 min. shock). The norm is 1-2 shocks/min. set in bursts. In addition, the criterion of shock to seminal emission (50) can be used.

ECSDY - The number of days of treatment with electro-convulsive shock (ECS), one shock per day via the ears.

COND - The controller referencing a number of classical conditioning paradigms. The unconditioned stimulus (UCS) is access to a sexually receptive female and the ensuing sexual behavior is the unconditioned response (UCR). The conditioned stimulus (CS) and the conditioned response (CR) vary. Both positive and negative reinforcement is used.

- 1 = a light is the CS.
- 5 = a loud bell is the avoidance CS.
- 10 = a pedal push (CR) is required for the female.
- 15 = a bar press (CR) is required for the female.
- 20 = an avoidance shock (CS) is given in the presence of the female; the male is tested later without shock in the same conditioning cage.
- 25 = the same as 20, but the male is tested later in a novel cage.
- 30 = no shock is given but tested in a novel cage - a conditioning control showing novel cage effects.

COPLIM - The controller for manipulation of copulatory performance.

- 1 = group testing - more than one male-female pair in one arena.
- 2 = testing pairs in adjacent arenas, one pair per arena.
- 3 = testing in a novel arena.
- 4 = testing in an arena one-half the size used previously.
- 5 = testing to exhaustion at least once a week.
- 6 = testing to 2 Es once a week prior to the test.
- 7 = testing to less than 4 Is/week prior to the experimental test.

COLLAR - The integer controller for the use of a large neck collar that prevents genital grooming, activated by a value greater than 0.

SEXSTIM - The controller for the copulatory stimulus allowed the male. The male can be exposed to a particular stimulus for a number of prior tests and then tested with a receptive female, or the particular stimulus may be presented to the male only on the experimental test. A few miscellaneous treatments are included also.

- 1 = a receptive female sexual stimulus (normal).
- 2 = early exposure to a receptive female.
- 5 = a receptive female stimulus of a different strain.
- 10 = another male as stimulus.
- 11 = previous experience with a male stimulus.
- 30 = handling during the test.
- 40 = observation by experimental male of a copulating pair immediately prior to testing.
- 60 = the stimulus of a female with a closed vagina.
- 75 = a nonreceptive female stimulus.
- 80 = a small male test stimulus.

85 = a small guinea pig test stimulus.
87 = an immobile (anesthetized) receptive female or a small rabbit stimulus.
90 = prior exposure to a receptive female, but prevented from physical contact (no contact female).
92 = exposure to female odors.
95 = left alone in a test arena prior to testing for long durations (40-60 minutes).

D. Sensory Variables.

NSEN(K) - The controller integer list for all sensory variables. Each of the 13 values for this controller designate a "yes" for that variable. A list of up to 12 values can be set for this array; any or all of the variables below may be called in any order or combination. The following variables deal with the removal of a sensory organ or the alteration of the perception of sensory stimuli.

1 = Olfactory bulbectomy (OBX): The removal of the olfactory bulbs, peduncle, or neural tissue adjacent and caudal to the bulbs.
2 = Anosmia: The removal of smell without damage to the brain. The nasal epithelium is scraped and a caustic fluid is introduced into the nasal passages with or without cutting the olfactory nerve.
3 = Blinding: The removal of sight by enucleation.
4 = Glansectomy: The removal of the sensitivity of the penis by surgically removing the glans penis.
5 = Penile bonectomy: The removal of some penile rigidity by surgical excision of the penile bone, usually prior to puberty.
6 = Penile nervectomy (PNX): The elimination of sensory and/or motor innervation to the penis and pubic area by sectioning the Pudendal, Pelvic, or the Dorsal Penile Nerve. (The CUT variable serves the same function with integer value > 0).
7 = Penile anesthesia: The nonsurgical removal of penile stimuli. A topical anesthetic (e.g. Lidocaine) is liberally swabbed on the penis prior to testing.
8 = Precopulatory experience: The experimental male is exposed to a copulating pair of rats but prevented from participating by containment in a clear vented box.
9 = Self-stimulation (SS): The male is implanted with an electrode in the ventrolateral thalamus ("pleasure center") and conditioned to bar press for stimulation. The stimulation continues to seminal emission before testing with a female.

10 = Noise: The copulating pair is exposed to a loud white noise during the test period.
11 = Multiple organ removal: Two or more sensory organs are removed or prevented from functioning; it includes any combination of OBX, anosmia, blinding, PNX, or cutting the facial (5^{th}) nerve.
12 = Facial (5^{th}) nerve cut: The cutting or sectioning of the nerve innervating the vibrissae and the skin of the snout.
13 = None: This value bypasses all of the above.

E. Major Gonadotropic Hormone Variables

In all cases where a dosage and duration of treatment variable exists for a particular hormone, both must have a designated value to operate effectively in the model.

CAST - The number of days after the removal of the testes.

CASTH - The number of minutes after castration.

CASTD - The males' age in days at the time of castration.

CRYPTD - The number of days after the testes were placed into the abdominal cavity (cryptorchidectomy).

DPC - The number of days between castration and the initiation of the injection of any hormone or drug. A value less than 5.0 represents a maintenance regime and a value of greater than 10.0 represents a recovery regime.

INJ1 - The integer controller for limits placed on the number of injections given or for a non-injection hormone delivery.

0 = A normal series of injections given at least once a day over a period of days.
1 = Only one injection is given, usually as a large dosage, and testing proceeds from that day onward.
5 = A small number of injections are given (2-10); the injections are spaced more than one day apart.
15 = Hormones are introduced by infusion, usually into the jugular vein.
20 = A silastic capsule containing the hormone is implanted under the skin (used for any hormone except testosterone, that has a separate variable).

DTT - The dosage (ug) of free testosterone given per day.

DTTP - The dosage (ug/day) of testosterone propionate.

DYTT - The number of days of treatment with free testosterone.

DYTTP - The number of days of treatment with TP.

TIMP - The dosage of testosterone given as the length in millimeters of a silastic capsule implant. (DYTT must be set along with this variable for treatment days.)

TA - The number of days of treatment with testosterone acetate

NTA - The integer controller for the injection of 10 mg of TA in a single injection (value > 0 sets it).

NTC - The integer controller for the injection of 10 mg of testosterone cyprionate in a single injection (value > 0 to set).

NTE - The integer controller for the injection of 10 mg of testosterone ethanate in a single injection (value > 0 to set).

DEB - The dosage (ug/day) of estradiol benzoate (EB).

DE1 - The dosage (ug/day) of estrone (E_1).

DE2 - The dosage (ug/day) of free estradiol (E_2).

DE3 - The dosage (ug/day) of estriol (E_3).

EBDY - The number of days of treatment with EB.

E1DY - The number of days of treatment with E_1.

E2DY - The number of days of treatment with E_2.

E3DY - The number of days of treatment with E_3.

E2DPDI - The number of days of treatment with estradiol dipropionate (use DEB for dosage).

F. Androgen Variables

If both duration and dosage variables exist for a particular androgen, both variables need to be designated.

DDHT - The dosage (ug/day) of free dihydrotestosterone (DHT).

DDHTP - The dosage (ug/day) of dihydrotestosterone propionate (DHTP).

DHTPDI - The number of days of treatment with either DHT form.

DAND - The dosage (ug/day) of androsterone in oil.

ANDDI - The number of days of treatment with androsterone.

DWAND - The dosage (ug/day) of androsterone in water.

DANDOL - The dosage (ug/day) of androsterone-diol in oil.

ANDOLDI - The number of days of treatment with androsterone-diol.

DTANDOL - The dosage (ug/day) of TD-androsterone-diol.

DHEPAND - The dosage (ug/day) of dehepiandrosterone.

HEPANDI - The number of days of treatment with dehepiandrosterone.

DDHEA - The dosage (ug/day) of dihydroepiandrosterone or epiandrosterone.

DAEOL - The dosage (ug/day) of 4-androstenediol.

D5AEOL - The dosage (ug/day) of 5-androstenediol.

AEOLDI - The number of days of treatment with either androstenediol.

DHOAEN - The dosage (ug/day) of 11β-hydroxy-androstenedione.

HOAENDI - The number of days of treatment with 11β-hydroxy-androstenedione.

DAAAOL - The dosage (ug/day) of 3α-androstanediol.

AAAOLDI - The number of days of treatment with 3α-androstanediol.

DBAAOL - The dosage (ug/day) of 3β-androstanediol.

BAAOLDI - The number of days of treatment with 3β-androstanediol.

DAAONE - The dosage (ug/day) of androstanedione.

AAONEDI - The number of days of treatment with androstanedione.

HTPDI - The number of days of treatment with 19-hydroxytestosterone propionate.

G. Pituitary and Nongonadal Hormone Variables, etc.

HPI - The number of hours after a hormone injection.

PLT - The systemic blood plasma level (ng/ml) for testosterone (T).

PLLH - The systemic blood plasma level (ng/ml) for LH.

PLFSH - The systemic blood plasma level (ng/ml) for FSH.

DLH - The dosage (ug/100 g BW) of LH injected per day.

DIULH - The dosage (IU/day) of LH injected.

LHMIN - The number of minutes after injection with LH.

DFSH - The dosage (ug/100 g BW) of FSH injected per day.

FSHMIN - The number of minutes after injection with FSH.

DPRL - The dosage (ug/day) of injected prolactin.

HCGD - The dosage (IU/day) of Human Chorionic Gonadotropin (HCG).

HCGM - The number of minutes after the injection of HCG.

DPROG - The dosage (mg/day) of progesterone.

DHPROG - The dosage (mg/day) of dihydro- or hydroxy-progesterone.

DPREG - The dosage (mg/day) of pregnenolone or pregnandione.

DHPREG - The dosage (mg/day) of dehydropregnenolone.

H - The number of days after hypophysectomy (removal of the pituitary gland).

HAX - The number of hours after adrenalectomy (removal of the adrenal glands).

THX - The number of hours after thyroidectomy (removal of the thyroid gland).

PINX - The number of days after pinealectomy (removal of the pineal gland).

STARV - The number of days of starvation (food deprivation). The minimum length of treatment for behavioral effect is six days.

H. Drug Variables

With the exception of FM, the drugs listed below are usually used in conjunction with testosterone in castrate males, and in a few cases with estrogen. To obtain a demonstration of anti-androgenic or anti-estrogenic effects over days of treatment, both drug and hormone variables must be designated.

1. Androgen mimetic drug

DFM - The dosage (mg/day) of fluoxymesterone (FM) injected.

DYFM - The number of days of treatment with fluoxymesterone.

2. Anti-androgen drugs

DCYA - The dosage (mg/day) of cyproterone acetate.

DFL - The dosage (mg/day) of flutamide.

DYFL - The number of days of treatment with flutamide.

DSH - The dosage (mg/day) of Shering-714.

3. Anti-estrogen drugs

DMER - The dosage (mg/day) of MER-25.

DCI - The dosage (mg/day) of CI-628.

DCLOM - The dosage (mg/day) of cis-clomiphene.

DICI - The dosage (ug/day) of ICI-46474.

4. Aromatase inhibitors (block the conversion of testosterone to estrogen)

DMET - The dosage (mg/day) of metopirone.

METOPDI - The number of days of treatment with metopirone.

DAGT - The dosage (mg/day) of aminoglutethimide (AGT).

AGTDI - The number of days of treatment with aminoglutethimide.

II. Preset Input Variable Values

All input variables and their increment variables are preset prior to any designation of values by the user. The total of all the preset values produce an output consistent with the response of a normal group of control males given no experimental or hormonal treatments. Therefore, the user need only designate those variables in which he has an interest. Increment variables do not exist for the integer controller variables. The input variable and its increment variable (contained within the BINC array) are listed below with the preset values established within the program.

input variable	value	increment variable	value
A. Intrinsic Variables			
ST	1	none	
SR	1.0	none	(internal operation)
NSR	5.0	BINC(2)	0.0
A	200.0	BINC(1)	7.0
YMON	6.0	BINC(4)	0.23
B. Test Variables			
TNO	2.0	BINC(8)	1.0
TDN	5.0	BINC(3)	0.0
LTPER	12.0	BINC(5)	0.0
TBT	7.0	BINC(7)	0.0
TMIN	99.0	BINC(9)	0.0
COPMIN	60.0	BINC(15)	0.0
SEXEXT	10.0	BINC(6)	1.0
NRACOND	3	none	
TDRAIS	35.0	BINC(10)	0.0
C. Experimental Manipulation Variables			
SCREEN	0	none	
EICI	0.0	BINC(11)	0.0
NEICI	0	none	
NPI	0.0	BINC(13)	0.0
EPEI	0.0	BINC(12)	0.0
NFRESH	0	none	

input variable	value	increment variable	value
ISHOCK	0	none	
ISS	0	none	
ECSDY	0.0	BINC(14)	0.0
COND	0	none	
COPLIM	0	none	
COLLAR	0	none	
SEXSTIM	0	none	

D. Sensory Variables (controller list)

NSEN(K) 13*13 (13 consecutive 13s)

E. Major Gonadotropic Hormone Variables

CAST	0.0	BINC(16)	0.0
CASTH	0.0	BINC(17)	0.0
CASTD	30.0	BINC(19)	0.0
CRYPTD	0.0	BINC(20)	0.0
DPC	0.0	BINC(18)	0.0
INJ1	0	none	
DTT	0.0	BINC(22)	0.0
DTTP	0.0	BINC(21)	0.0
DYTT	0.0	BINC(24)	0.0
DYTTP	0.0	BINC(23)	0.0
TIMP	0.0	BINC(25)	0.0
TA	0.0	BINC(26)	0.0
NTA	0	none	
NTC	0	none	
NTE	0	none	
DEB	0.0	BINC(27)	0.0
DE1	0.0	BINC(28)	0.0
DE2	0.0	BINC(29)	0.0
DE3	0.0	BINC(30)	0.0
EBDY	0.0	BINC(31)	0.0
E1DY	0.0	BINC(32)	0.0
E2DY	0.0	BINC(33)	0.0
E3DY	0.0	BINC(34)	0.0
E2DPDI	0.0	BINC(35)	0.0

F. Androgen Variables (all input and increment variables preset at 0.0)

input	increment	input	increment
DDHT	BINC(37)	DAEOL	BINC(47)
DDHTP	BINC(36)	D5AEOL	BINC(49)
DHTPDI	BINC(38)	AEOLDI	BINC(48)

input	increment	input	increment
DAND	BINC(39)	DAEONE	BINC(50)
ANDDI	BINC(40)	AEONEDI	BINC(51)
DWAND	BINC(59)	DHOAEN	BINC(52)
DANDOL	BINC(60)	HOAENDI	BINC(53)
ANDOLDI	BINC(61)		
DTANDOL	BINC(63)	DAAAOL	BINC(41)
		AAAOLDI	BINC(42)
DHEPAND	BINC(54)	DBAAOL	BINC(43)
HEPANDI	BINC(55)	BAAOLDI	BINC(44)
DDHEA	BINC(56)		
		DAAONE	BINC(45)
HTPDI	BINC(58)	AAONEDI	BINC(46)

G. Pituitary and Nongonadal Hormone Variables, etc. (all of the input and increment variables are preset at 0.0)

HPI	BINC(64)	DPRL	BINC(72)
PLT	BINC(77)	DPROG	BINC(73)
PLLH	BINC(78)	DHPROG	BINC(74)
PLFSH	BINC(79)		
		DPREG	BINC(75)
DLH	BINC(66)	DHPREG	BINC(76)
DIULH	BINC(67)		
LHMIN	BINC(65)	H	BINC(80)
		HAX	BINC(81)
DFSH	BINC(68)	THX	BINC(82)
FSHMIN	BINC(69)	PINX	BINC(83)
HCGD	BINC(70)	STARV	BINC(99)
HCGM	BINC(71)		

H. Drug Variables (all of the input and increment variables are preset at 0.0)

DFM	BINC(84)	DMER	BINC(88)
DYFM	BINC(85)	DCI	BINC(94)
		DCLOM	BINC(95)
DCYA	BINC(89)	DICI	BINC(96)
DFL	BINC(86)		
DYFL	BINC(87)	DMET	BINC(90)
DSH	BINC(98)	METOPDI	BINC(91)
		DAGT	BINC(92)
		AGTDI	BINC(93)

APPENDIX B

APPENDIX B

Standard Functions

1. Straight line :

$$y = a \cdot x + b$$

2. Curvilinear functions :

   a. Functions showing a decelerating increase with increasing values of "x".

      1) $y = \sqrt{a \cdot x}$

      2) $y = \frac{a \cdot x}{x + b}$

      ("a" controls the rate of increase and "b" establishes the maximum amplitude)

   b. Logarithmic functions (show a decelerating increase):

      1) Natural logarithm. (base "e")

      $$y = a \cdot \ln(x)$$

      2) Common logarithm (base 10):

      $$y = a \cdot \log(x)$$

   c. The Inverse (showing a decelerating decrease with increasing " x")

   $$y = \frac{a}{x}$$

3. Exponential Functions :

   a. Functions of "x" raised to an exponent.

   $y = a \cdot x^n$ (general form)

   $y = a \cdot x^2$ or $y = a \cdot x^3$ (usual specific forms)

   b. Functions of "e" :

      1) $y = A \cdot e^{a \cdot x}$ (accelerating increase)

      2) $y = A \cdot e^{a/x}$ (decelerating decrease)

      3) $y = A \cdot e^{-a(x-z)}$ (decelerating decrease)

Standard Functions (cont.)

4) $y = A(1 - e^{-a(x-z)})$ (decelerating increase)

("A" is the amplitude - in the case of the negative exponent the curve ranges between 1.0 and 0.0 with A=1.0.
"a" is the rate function controlling the rate of acceleration or deceleration.
"z" shifts the entire curve to the right or left along the "x" axis.)

4. Functions with contained exponents:

a. Sigmoid functions ("S" shaped curves) :

1) $$y = A_o + (A_1 - A_o)\left[\frac{1}{1 + (c/x)^a}\right]$$

2) $$y = A_o + (A_1 - A_0)\left[1 - \frac{1}{1 + (c/x)^a}\right]$$

(The curve ranges from the minimum value, A_0, to the maximum value, A_1, passing through the midpoint value of "y" at the "c" value.
The curve ranges from low to high (1) or from high to low (2). Again "a" controls the rate of change.)

b. Other functions :

1) $$y = (x/c)^a$$

(shows accelerating increase, if a>1, and
decelerating increase, if a<1. "c" is a constant)

2) $$y = \sqrt{1 - (x/c)^a}$$ (accelerating decrease)

$$y = 1 - \sqrt{(x/c)^a}$$ (decelerating decrease)

(Both equations range between 0 and 1, where "c" establishes the value of "x" for y=0)

5. Useful alterations of the above equation forms.

a. The Inverse of a function - the inverse is useful for equations ranging between 0 and 1. The inversion alters a curve starting at 0 and increasing to one starting at 1 and decreasing, but with the same rate of change and shape.

$$y = 1 - f(x)$$

b. The adjustment for the minimum value of "y".

$$y = A(f(x)) + b$$

(The minimum value of the function is now "b", and its maximum value equals "A + b" .)

APPENDIX C

APPENDIX C

The Direction of Effect for the Behavioral Measures in Response to the Input Variables and the Direction for the Penile Measures with the Hormonal Variables are Included.[ab]

Intrinsic Var.		PE	PI	PM	IL	IF	EL	PEI	EF
A (Age)	- young	-	*	*	+	+	+	+	-
	adult	0	0	0	0	0	0	0	0
	old	-	-	-	+	-[c]	+	+	-
TDN	- night	*	*	*	±[c]	0	±	±	0
	day	-	-	*	+[c]	+	+	+	-
TBT	(test interval)	-	*	*	+	0	+	+	-
SEXEXT	(sex experience)	0	0	*	+	0	+[c]	0	-
	- old males	-	-	*	"	"	"	"	"
NRACOND	- Isol.	-	-	-	-	0	-[c]	0	0
	Cohab.	+	+	+	-	0	0	0	0
	Seg.	0	0	0	0	0	0	0	0
SCREEN	- Cohab.	-	*	*	0	0	*	*	0
	Seg.	-	*	*	0	0	-	*	0
Behavior & Stimulus Var.									
EICI	- 1I only	-	*	*	-	-	*[c]	-	-
	all Is	*	*	*	-	-	+	-	*
	all Is + Sat.	*	*	*	*	*	*	+	*
EPEI		*	*	*	-	+	+	0	0
NFRESH= 1	- at E, exp.	*	*	*	0	0	-	0	0
	inexp.	*	*	*	"	"	"	+	"
10	- at Sat.	+	+	+	+	+	0	-	+
25	- at E + Sat.	+	*	+	*	0	*	*	*
ISHOCK=10	- exp.	0	0	0	-	0	-	-	+
	inexp.	+	+	+	-	0	*	*	*
	& bar press	*	*	*	0	-	0	-	*
5	- high shock	-	-	-	+	-	*	*	*
ECSDY		+	0	0	+	-	-	+	*

APPENDIX C (Cont.)

Beh. & Stim. Var.(cont.)	PE	PI	PM	IL	IF	EL	PEI	EF
COND = 1 (conditioning)	*	*	*	*	+	*	-	0
5	*	*	*	*	+	+	+	-
10	0	*	*	*	0	0	0[c]	0
15	*[c]	*[c]	*	+	0	0	-[c]	*
20	-[c]	-[c]	*	-	-	-	*	*
25	0	0	*	0	-[c]	0	*	*
30	-	0	*	-	0	*	*	*
COPMIN = 1 - Group Ts.	+	*	*	*	-[c]	-[c]	0	+
2 - Adj. Ts., Ad.	+	*	*	*	-[c]	0	0	+
" " Old	+	*	*	*	0	0	0	+
4 - halfcage	-	0	0	*	-	*	*	-
COLLAR	*	*	*	-	0	0	0	*
SEXSTIM = 1 (sexual stim.)	-	*	*	*	-	*	*	*
2	-	0	0	*	*	*	*	*
5	*	+	*	*	+	*	*	*
10	-	0	0	*	-	*	*	*
11	-	-	-	*	-	*	*	*
30 - Adult	*	*	*	0[c]	0	-	0	0
Old	*	*	*	+[c]	-	-	-	+
40	*	*	*	-[c]	0	-	0	*
60	-	0	0	0	-	-	0	*
75	-	-	-	*	-	*	*	*
80	-	-	-	*	-	*	*	*
85	-	-	-	*	-	*	*	*
87	-	-	-	*	-	*	*	*
Sensory Var. (NSEN)								
1 (OBX)	-	-0	0	+	-	+	+	-
2 (Anosmia)	-	-	0	+	-	+	+	-
3 (Blind)	-	-	-	+	0	+	-	0
4 (glans X)	0	0	0	*	*	+	*	*
5 (Penile bone X)	-	-	0	*	-	*	*	-
6 (PNX) - exp. males	-	-	-	+	0	+	+[c]	-
inexp. males	-	-	-	+	0[c]	+	+[c]	-
EB + DHT	0	0	0	0	+	*	*	*
DHT	-	-	-	*	*	*	*	*
7 (Penile Anesthesia)	-	-	0	+	-	+	-	*
9 (Self Stimulation)	*	*	*	0	0	0	0	*

APPENDIX C (Cont.)

Sensory Var. (cont.)	PE	PI	PM	IL	IF	EL	PEI	EF	PP	PW
10 (noise)	*	+	*	+	*	*	*	*		
11 (mult. sense X)	-	-	-	+	-	*	*	*		
12 (5th nerve cut)	-	-	-	+	0	*	*	0		
Gonadotropins[d]										
CAST (days postcastration)	-	-	-	+	-	+	+	-	-	-
CASTD (Age at cast.)	-	-	-	*	*	+	+	*	*	*
T - R - dose	+	+	+	*	*	-[e]	-[e]	*	*	+
days	+	+	+	*	*	*	*	*	*	+
TP - M - dose	+	+	+	-	+	-[e]	-	+[e]	+	*
days	-	0	0	0	0	0[e]	0[e]	0	-	*
R - dose	+	+	+	-	+	-[e]	-[e]	+[e]	+	+
days	+	+	+	0	0	*	*	+	+	+
TIMP - MR - dose	+	+	+	*	+	-[e]	-	*	*	+
days	0+	0+	0+	*	*	*	*	*	*	*
- intact (young)	+	+	+	*	*	*	*	*	*	*
TA - MR	+	+	*	*	+	-[e]	*	*	+	*
TC - R	+	+	*	*	*	*	*	*	*	*
TE - R	+	+	*	*	*	*	*	*	*	*
EB - inexp. - R - dose	+[c]	+	+	0	+[c]	-[c]	-[e]	*	*	*
days	+	+	+	*	+[c]	*	0	*	*	*
exp. - M - dose	+	+	+	-[e]	+[c]	+	-	+[c]	*	*
days	-	-	0[e]	0	-	+	0	*	*	*
exp. - R - dose	+	+	+	*	+[c]	+[c]	-	0	+[c]	+
days	+	+	+	*	+	*	*	*	*	*
intact	0	0	+	+	*	+	+	*	*	*
E2	0	0	+	*	*	*	*	*	*	+
E2DP	+	*	*	*	*	*	-[e]	*	*	*
E1	0	0	+[c]	*	*	*	*	*	*	+
E3	0	0	+[c]	*	*	*	*	*	*	0
EB + TTP (vs. TTP control)	+	+	+	0	0	0	0	*	0	0

APPENDIX C (Cont.)

Androgens [d]			PE	PI	PM	IL	IF	EL	PEI	EF	PP	PW
DHT(P)	- M -	dose	+[e]	+[e]	+[e]	-	+[e]	-[e]	0	+[c]	+	*
		days	-	-	-	0	-[c]	0	0	*	*	*
	R -	dose	+[e]	+[e]	+[e]	-	+	-	0	0	+	+
		days	+	+	+	0	*	*	*	0	*	*
EB + DHT(P)	- R -	dose	+	+	+	-[e]	+[e]	-[e]	-	+	+	*
		days	+	+	+	0[e]	*	*	*[e]	0	*	*
E2 + DHT	- R -	dose	+	+	+	-[c]	*	-[c]	-	*	*	+
E1 + DHT	- R -	dose	+	+	+	-	*	-	*	*	*	+
E3 + DHT	- R -	dose	+	+	+	*	*	*	*	*	*	+
TP + DHT	- MR -	days	+	+	+	-[e]	0[e]	-[e]	-[e]	*	0[e]	0[e]
AEOL	- R -	dose	+	+	+	-	+[e]	-[e]	-[e]	*	*	+
AEONE	- M -	days	-	0	0	0[e]	*[e]	0[e]	-[c]	*	+	*
	R -	dose	+	+	+	-[e]	+[e]	-[e]	-	*	*	+[e]
AND	- M		0	*	*	*	*	*	0	*	+	+
	R		0	0	0	*	*	*	*	*	*	+
HEPAND	- R		0	+	+	*	*	*	*	*	*	*
HOAEN	- MR		0	+	+	*	*	*	-	*	0	*
AAONE	- M		+	*	*	*	*	*	-	*	*	*
	R		0	0	+	*	*	*	*	*	+	*
AAAOL	- M		+[c]	*	*	*	*	*	-[c]	*	*	*
	R		0	0	+	*	*	*	*	*	+	*
BAAOL	- M		0	*	*	*	*	*	0	*	*	*
	R		0	0	+	*	*	*	*	*	+[c]	*
HTP	- M		+	*	*	*	+[c]	*	-[e]	*	0	*
DHTP + BAAOL	- R (vs. DHT)		+	*	+	*	0[e]	0	0	*	0[e]	*
DHTP + HTP	- M		+[c]	*	*	*	*	*	-	*	*	*

APPENDIX C (Cont.)

Nongonadal Var.	PE	PI	PM	IL	IF	EL	PEI	EF	PP	PW
H - Hypophysectomy	*	*	*	-	0	*	*	*	*	*
HAX - Adrenalectomy	0	0	0	0	0	+	0	*	*	*
LH + FSH	0	0	0	0	0	0	0	*	*	*
Progesterone	*	*	*	*	0	*	*	*	*	*
Prog. + EB	*	*	*	0	0	0	0	*	*	*
Prog. + TP	*	*	*	0	0	*	*	*	*	*
Drug Var.										
FM[d] - M - dose	*	*	*	*	+[e]	*	*	*	*	*
days	+	+	+	-	+[e]	-	0	+	+[e]	*
FM + EB	+	+	+	*	+	*	*	+	*	*
FM + PNX - M - dose	*	*	*	*[e]	+	*	*	*	*	*
days	+	+	+	-[e]	+[e]	-	-	+	*	*
CYA intact -	0	*	*	*	-[c]	*	0	*	0	*
cast. - R	0	0	0	0	+[c]	0	0	*	+	0
M	+	*	*	*	*	*	-	*	+	0
+ TP - MR	0	*	*	0	0	0	0	*	-	0
+ EB - R	0	0	0	*	*	*	*	*	+	0[c]
+ DHT - R	0	0	0	*	*	*	*	*	-[c]	-[c]
+ EB + DHT - R	0	-	-	*	*	*	*	*	0	-[c]
FL intact	0	0	0	0	-[c]	*	0	*	*	*
cast. - R	0	0[c]	0	*	-[c]	0	0	*	0	0
+ TP - R	-	-[c]	0	0	-[c]	0	0	*	-	-
SH intact	-	*	*	*	*	*	*	*	*	*
MER cast. - R	0	0	0	*	*	*	*	*	0	0
+ TTP - R	0	0	0	-[c]	0	-	0	*	0	0
+ DHT - R	+	*	*	*	0	0	0	*	*	*
CI cast. - R	0	0	0	*	*	*	*	*	*	*
+ TP - MR	-	-	-	*	0	0	*	*	*	*
CLOM + TP - R	0	0	0	0	0	0	0	*	*	*
ICI + TP - R	-	-	-	+[c]	0	0	0	*	*	*

APPENDIX C (Cont.)

Drugs (cont.)	PE	PI	PM	IL	IF	EL	PEI	EF	PP	PW
MET + TP - R	0	0	0	0	0	-[c]	+[c]	*	*	*
AGT + TP - R	-	-	-	(no Is or Es occurred)						
AAONE + TP - R	0	0	0	0	0	0	0	*	*	*

a - The symbols refer to the direction of the E/C ratios:
(+) = a ratio of $r > 1.0$,
(-) = a ratio of $r < 1.0$,
(0) = no change from the $r = 1.0$ ratio,
(*) = indicates the lack of any supporting data.

b - see Appendix A for descriptions of the input variables.

c - The effect was reported as statistically nonsignificant ($p > .05$) but the model provided an effect.

d - E/C ratios refer to (cast. + hormone)/ cast., unless intact males were utilized. The symbol M refers to a maintenance regime and the symbol R refers to a recovery regime.

e - The response was equivalent to that of intact males at the reported dosages.

SEXUAL BEHAVIOR

AND

PENILE

BIBLIOGRAPHY

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